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PLATELET INDICES – CAN THEY ASSESS BLEEDING RISK IN PATIENTS OF IMMUNE THROMBOCYTOPENIC PURPURA? – A PROSPECTIVE STUDY

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ABSTRACT Immune thrombocytopenic Purpura (ITP) is an autoimmune disease characterized by low platelet counts and an increased risk of bleeding. Its clinical manifestations are highly variable. Even at the same platelet count level, patients can have bleeding manifestations that can range from none to severe. The goal of therapy is to treat or prevent bleeding. The relation between the various bleeding manifestations with the platelet count and other platelet volume indices in ITP patients' remains poorly characterized. In this study 28 patients were enrolled, both male and female, aged 5-84 years. Bleeding risk was calculated by using IBLS scale. No bleeding was observed among 53.6% of ITP patients and severe bleeding was observed in 28.6%.However, no statistically significant (p>0.05) difference in platelet parameters among grades of bleeding in ITP patients was found.

KEYWORDS : Immune thrombocytopenic purpura, bleeding risk, platelet indices, IBLS scale

INTRODUCTION

Platelets are essential for primary hemostasis and any variation in their count and function can manifest in the form of bleeding. Normal count of platelets in the circulatory blood ranges from 1,50,000-3,00,000/µL. Counts below 100,000/µL are known as thrombocy topenia.[1] Patho-physiologically, it is classified under 4 main processes: A) Artifactual thrombocytopenia B) Increased platelet destruction (hyperdestructive thrombocytopenia) C) Decreased platelet production and D) Abnormal pooling of platelets.[2] Idiopathic Thrombocytopenic Purpura (ITP) is one of the most common causes of hyperdestructive thrombocytopenia which can occur in both children and adults. The patients of ITP are defined according to the American Society of Hematology Guidelines,[3] as those who on the basis of medical history, physical examination and complete blood test show isolated thrombocytopenia without any other underlying disease, with or without bone marrow examination showing normal or increased megakaryocytes with poor platelet separation and normal other hemopoietic lineages.[4]

ITP is generally a self-limiting disease in case of children whereas in adults it may follow a chronic course. It has an incidence of 3.3/100,000 adults per year and a prevelance of 9.5 per 100,000 adults.[5]

There can be different bleeding manifestations of ITP and they can vary from common symptoms like easy bruising to rare and life threatening conditions like intracranial hemorrhage. Other symptoms can be petechial hemorrhages, mucosal bleeding, epistaxis etc. bleeding manifestations of immune thrombocytopenic purpura are generally purpuric type.[1]Studies have shown that there is an increased rate of mortality due to bleeding in these patients and therefore proper understanding and assessment of bleeding risk in the patients of ITP can lay an important foundation for the basis of therapy in them.[5]The ITP bleeding scale (IBLS) which comprises of 11 site specific grading system was used in this study. The range varies from 0 (none) to 2 (marked bleeding). It assesses 9 anatomical sites (skin, oral, epistaxis, gastrointestinal, urinary, gynaecological, pulmonary, intracranial hemorrhage, subconjunctival hemorrhage) on the basis of history and 2 sites (skin and oral) on the basis of examination. Current assessment and regular use of bleeding scale along with its correlation with laboratory parameters i.e. platelet count and IPF can help in reducing mortality due to ITP. Also, it can reduce unnecessary blood transfusions in these patients.[6] Thus, the present study was done to assess bleeding risk in patients of ITP on the basis of clinical parameters and platelet indices.

AIMS AND OBJECTIVE

1. To assess the bleeding risk in patients of ITP by using IBLS scale.
2. To evaluate platelet indices in the patients of ITP.
3. To find any correlation between the platelet indices and bleeding risk in the patients of ITP.

METHODS

The study was conducted at Regency Hospital Ltd. Kanpur, a Multi-super speciality tertiary care hospital. Both IPD and OPD patients with thrombocytopenia (Platelet count <1,00,000/cumm) and who were diagnosed as ITP on the basis of clinical and haematological investigations (both peripheral blood and bone marrow examination) were included in the study. The prospective study was conducted over a period of 2 years (June 2018-July 2020).

A total of 28ITP patients were enrolled, both female and male, with ages ranging from 5-84 years. After obtaining their informed consent, they were inquired about their clinical history and their socio-demographic information. Brief clinical data was noted which included age, presenting symptoms, any significant history of past or present bleeding, past hospitalization and drug medication. All the patients were assessed for bleeding risk based on history and clinical examination based on IBLS scale.

Table-1 : The Itp Bleeding Score Assessment[6]

SITE	GRADE 0	GRADE 1	GRADE 2
Skin (physical examination [PE])	none	1-5 bruises and/or scattered petechiae	>5 bruises with size >2cm and/or diffuse petechiae
Oral(PE)	none	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin(Hx)	none	1-5 bruises and/or scattered petechiae	>5 bruises with size >2cm and/or diffuse petechiae
Oral(Hx)	none	1 blood blister or >5 petechiae or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min

Epistaxis	none	Blood when blowing nose and/or epistaxis<5 min (per episode)	Bleeding >5 min(per episode)
Gastrointestinal (GI)	none	Occult blood	Gross blood
Urinary(U)	none	Microscopic (+ve dipstick)	Macroscopic
Gynaecological (GYN)	None (normal period)	Spotting (not at time of normal period)	Bleeding (>spotting not at time of period)
Pulmonary	none	N/A	yes
Intracranial hemorrhage	none	N/A	yes
Subconjunctival haemorrhage	none	yes	N/A

Peripheral blood samples were collected by venipuncture by the same technical staff responsible for the collection of routine blood samples and using the standard operating procedures in 3 ml Vacutainer EDTA K2 tubes.[7] The samples were run in fully automated hematolog yanalyzer Sysmex XN-1000 with established reference ranges for the parameters, based on the principle of Flow Cytometry. The routine haematological parameters - Hemoglobin, TLC, DLC, MCV, MCH, MCHC and platelet counts alongwith the platelet indices - MPV, PDW, P-LCR, PCT and Immature Platelet Fraction (IPF) were recorded in each patient. All the blood samples were analyzed within 4 hours of collection. The performance of the instrument was monitored by running quality control materials. All the methods applied as mentioned in material and methods were routinely done in such patients and no unethical test or procedure was employed during this study. Patients did not bear any additional financial burden due to study. Hence, this study was ethically justified.

The results were presented in frequencies, percentages and mean ± SD. The Chi-square test was used to compare categorical variables. The Unpaired t-test/Mann-Whitney U test was used to compare continuous variables. The one way analysis of variance (ANOVA) followed by Tukey's post-hoc tests was used to compare study parameters among grades of bleeding. The receiver operating curve (ROC) analysis was carried out. The area under the curve (AUC) with its 95% confidence internal (CI) was calculated. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with its 95% CI were calculated. The p-value<0.05 was considered significant. All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA).

RESULTS

Grades of bleeding were correlated with platelet count and platelet volume indices (MPV, PDW, P-LCR,PCT and IPF) to assess the bleeding risk. Majority of the patients had no bleeding. Severe bleeding (Grade 2) was seen in skin on physical examination in 14% of cases followed by 3% each in oral (on PE), skin (on Hx), oral (on Hx), and urinary (on Hx). No bleeding was documented in Gastrointestinal, gynecological, pulmonary, intracranial hemorrhage or subconjuctival hemorrhage.

Table-2: Bleeding Risk Assessment Done On 28 Patients Of Itp. 11 Site Specific Bleeding Categorized Into 3 Grades.

Site	Grade 0 (Nobleeding)	Grade 1(Mild/Moderate bleeding)	Grade 2(Severe bleeding)
Skin [physical examination (PE)]	22 (78%)	2 (7%)	4 (14%)
Oral (PE)	27 (96%)	--	1 (3%)
Skin (Hx)	27 (96%)	--	1 (3%)
Oral (Hx)	27 (96%)	--	1 (3%)
Epistaxis	25 (89%)	3 (10%)	--
Gastrointestinal (GI)	28 (100%)	--	--
Urinary (U)	27 (96%)	--	1 (3%)
Gynecological (GYN)	28 (100%)	--	--
Pulmonary	28 (100%)	--	--
Intracranial haemorrhage	28 (100%)	--	--
Subconjunctival haemorrhage	28 (100%)	--	--

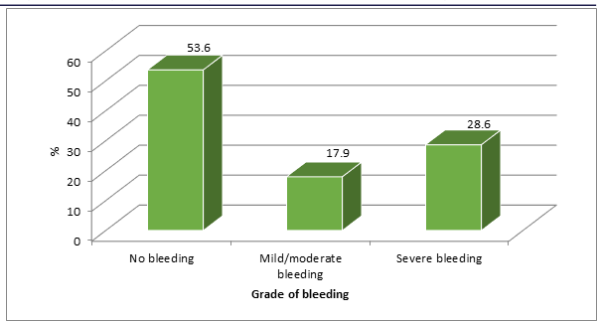

Fig. 1 Shows The Distribution Of Grades Of Bleeding Among ITP Patients. No Bleeding Was Seen In 53.6% Of ITP Patients And Severe Bleeding Was Seen In 28.6%.

Table-3 Compares ITP Patients' Age With Grades Of Bleeding. No Statistically Significant P>0.05) Difference Was Observed

Bleeding	Age in years (Mean±SD)
No bleeding	49.13±20.50
Mild/moderate bleeding	24.20±33.52
Severe bleeding	19.50±17.62
p-value[1]	0.06

[1]Kruskal-Wallis test

Table -4 Compares grades of bleeding Among Males And Females In Itp Patients. No Statistically Significant (p>0.05) Difference Was Observed.

Gender	No bleeding (n=15)		Mild/moderate bleeding (n=5)		Severe bleeding (n=8)		p-value[1]
	No.	%	No.	%	No.	%	
Male	9	60.0	5	100.0	4	50.0	0.16
Female	6	40.0	0	0.0	4	50.0	

[1]Chi-square test

Table-5: Comparison Of Various Platelet Parameters With Grades Of Bleeding In ITP Patients

Parameters	No bleeding (n=15)	Mild/moderate bleeding (n=5)	Severe bleeding (n=8)	p-value[1]
Platelet count	42.33±31.97	28.60±19.54	18.25±25.08	0.11
MPV	13.84±1.75	12.84±1.96	13.60±1.66	0.57
PDW	17.78±1.4	18.12±1.23	18.51±1.29	0.37
P-LCR	40.42±11.44	34.94±13.85	26.11±12.44	0.06
PCT	0.04±0.03	0.04±0.01	0.10±0.18	0.39
IPF	19.52±15.45	13.72±5.70	23.40±12.30	0.45

[1]Kruskal-Wallis test

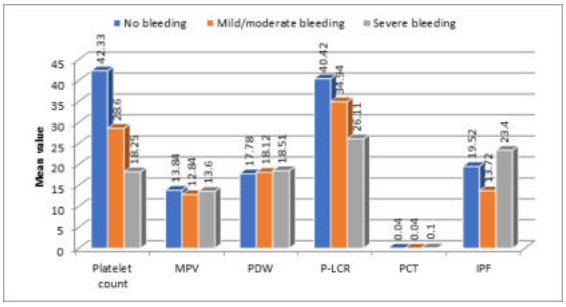

Fig. 2: Comparison Of Platelet Parameters With Grades Of Bleeding In Itp Patients

Table-5 & Fig. 2compares platelet count and various platelet indices among grades of bleeding in ITP patients. There was no statistical significant (p>0.05) difference in parameters among grades of bleeding in ITP patients.

DISCUSSION

Immune thrombocytopenic Purpura (ITP) is an autoimmune disease characterized by low platelet counts and an increased risk of bleeding. Its clinical manifestations are highly variable. Even at the same platelet count level, patients can have bleeding manifestations that can range from none to severe.[8]

It had been observed that rates of severe bleeding are highly variable across the studies not only because of differences in study designs, but also because of the lack of a universal, standardized bleeding measurement tool.[8]

Page et al[6] (2007) conducted a study to assess bleeding risk on the basis of ITP Bleeding Scale (IBLS) by assigning a bleeding severity score from 0 (no bleeding) to 2 (marked bleeding) at 9 anatomical sites by history (skin, oral, epistaxis, gastrointestinal, urinary, gynecologic, pulmonary, intracranial, and subconjunctival), and 2 anatomical sites by physical examination (skin and oral).[6]

Comprising 11 site-specific distinct grades, the IBLS gave a denser picture of bleeding symptoms than previously published scales (Buchanan et al[9], 2002). Incorporating both History (HX) and Physical Examination (PE) enabled the improved detection of rapidly fluctuating signs and symptoms in their study.

Similar to the study conducted by Page et al[7] (2007), the present study also showed that majority of the patients of ITP did not present with bleeding symptom at any platelet count. However, the present study had more patients presenting with severe bleeding (28%) as compared to moderate bleeding(18%).

The present study had 28 patients of ITP, where only 3 patients (11%) had epistaxis for less than 5 min, 2 patients(7%) had less than 5 petechiae on the basis of physical examination, 5 patients(18%) had more than 5 petechiae on the basis of physical examination, gum bleeding lasting for more than 5 min was observed in 2 patients(7%) and only 1 patient(3%) presented with gross hematuria. None of the patients reported gastrointestinal, gynecological, pulmonary, intracranial hemorrhage or subconjunctival hemorrhage. Rest 54% did not present any kind of bleeding.

Hato et al[10](2020) observed that the frequency of purpura and gingival bleeding increased modestly with age and the frequency of epistaxis was independent of age. In the present study, the bleeding symptoms were independent of age.

He also assessed that the most frequent manifestation in ITP was purpura (64.8%) followed by gingival bleeding(20.27%), epistaxis (12.49%), hematuria (6.21%), melena (6.10%), and ICH (1.14%). The frequency of purpura increased linearly with thrombocytopenia in their study exhibiting a strong negative correlation with platelet count. Bizzoni et al[11](2006) reported that risk of bleeding was more among females. The present study showed no such correlation between bleeding and gender.

The correlation between bleeding and platelet count in ITP has been examined in previous studies that showed increased bleeding below a platelet count of $20X10^9$/L. (Buchanan et al[9][2002]). Piel-julian et al[12] (2018) also found that platelet count is one of the main risk factors for bleeding in newly diagnosed ITP adults.

However, the present study failed to show any significant correlation ($p>0.05$) between platelet count and bleeding. In many patients platelet count was below $20X10^9$/L and still there was no sign of bleeding.

This study included other platelet indices (MPV, PDW, P-LCR, PCT and IPF) apart from platelet count, to find out any correlation between these parameters and risk of bleeding. Like age, gender and platelet count, no significant correlation between the platelet indices and different grades of bleeding ($p>0.05$) could be found. Page et al study also demonstrated that platelet count and large platelet count were poor indicators of bleeding in marked thrombocytopenia.

The bleeding risk assessment evaluation amongst the ITP patients has been done by few authors, hence adequate literature was not available for comparison. Moreover, amongst the platelet indices parameters, only platelet count was used for assessing the risk in previous studies. This may be one of the initial studies which also evaluated MPV, PDW, P-LCR, PCT and IPF with bleeding risk. The smaller sample size and assessment of the patients only on one visit for the assessment of bleeding risk in ITP were a few limitations of the present study. Many patients were lost during the follow up and hence assessment which was made on the first visit to the hospital was taken into consideration. Therefore the results of this study need to be further confirmed by larger studies in the future.

CONCLUSION

Bleeding risk assessment in ITP patients cannot be completely done on the basis of platelet count and platelet indices. Also, there is no age wise and gender based differences in bleeding risk. However, more studies with larger sample size need to be done in near future for further evaluation of bleeding risk assessment.

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