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Original Research Article

Role of platelet distribution width and plateletcrit in assessment of nonthrombocytopenic preeclampsia and eclampsia in a tertiary care hospital of Odisha: an observational study

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ABSTRACT

Background: Preeclampsia (PE) is a major cause of maternal and foetal morbidity and mortality in pregnancy. A decreased platelet count is observed during the progression of preeclampsia, and is considered a marker of the severity of preeclampsia. Considering the role of the PDW, PCT and platelet indices during the disease, the aim of this study was to evaluate the feasibility of using platelet indices as a severity marker for PE.

Methods: This was a prospective, observational study, hospital-based study, from 2017-19 with 400 pregnant women being included on the basis of a predefined inclusion and exclusion criteria, through antenatal clinic, and labour room of the department of obstetrics and gynecology, S. C. B. Medical College, Cuttack, Odisha, India.

Results: Study found that platelet count and plateletcrit showed a significant negative correlation with MAP whereas platelet distribution width showed a maximum positive correlation. In the preeclampsia group, subjects with PCT <0.22% were at risk of developing severe disease with a sensitivity of 53.5% and a high specificity of 85.5%. The AUC of 0.75 showed that it has a good predictability. In the eclampsia group, subjects with PCT <0.16% had a risk of developing severe disease with a specificity of 73.7%. The AUC 0.9 shows PCT to be a good predictor for assessing severity of eclampsia.

Conclusions: This study suggests that platelet distribution width and plateletcrit are useful in risk evaluation of preeclampsia. These are a valid measurement tool to predict the severe progression of PE even when normal platelet counts are observed.

Keywords: Eclampsia, Plateletcrit, Platelet distribution width, Platelet indices, Preeclampsia

INTRODUCTION

Preeclampsia (PE) is a major cause of maternal and foetal morbidity and mortality in pregnancy. Preeclampsia is a multi-organ disease with an unknown aetiology, and many studies have investigated this condition. Although the exact cause of PE is not fully understood, certain factors have been attributed to it which includes changes in placental perfusion, with changes in the coagulation system, endothelial dysfunction, fibrin deposition, and platelet activation.¹ A decreased platelet count is observed during the progression of preeclampsia, and is considered a marker of the severity of preeclampsia. Though preeclampsia is defined by hypertension and proteinuria, transition of the coagulation function between platelet and endothelial vascular cells is believed to play an important role in the pathogenesis of PE.²

Normal platelets are present in an inactive form in the blood stream and can be activated if in contact with exposed endothelial wall. Abnormal active platelets are involved in the pathogenesis of many diseases with thrombotic components like PE. Platelet activity is correlated with change in platelet volume, the larger platelets are haemostaticaly more active and thrombogenic than smaller ones. Mean platelet volume (MPV), platelet distribution width (PDW), and plateletlarge cell ratio (P-LCR) are volume measuring platelet indices; which increase during platelet activation.¹

The PDW represents the heterogeneity in platelet morphology due to the presence of large platelets along with normal-sized platelets. It can be clinically related to platelet activation, large platelets are usually more reactive than smaller ones due to increased number and size of the pseudopodia, leading to increase in the PDW value.³ The PDW is calculated by measuring the width of the size distribution curve (in femtoliters (fl)) at the 20% level when the peak distribution curve is taken as 80% or 100%.⁴

Plateletcrit depicts total platelet mass, analogous to the haematocrit for erythrocyte. It has been proposed that haemostatic ability of platelet depends not only on number of platelets but also on the size of platelet because large platelets are functionally more active than small platelets. Plateletcrit being a product of platelet count and Mean Platelet Volume (MPV) reflects changes in both the parameters, i.e., number and size of platelets. Therefore, plateletcrit or total platelet mass is more indicative of haemostatic capability of platelets than the platelet counts alone.

However, the circulating blood platelet plays a crucial role in maintaining normal haemostasis. It is the circulating platelet mass, not the platelet count, which is regulated by the body. As plateletcrit is an indicator of platelet activity in blood, low plateletcrit reflects low platelet activity.⁵ It has been found that plateletcrit can be used instead of platelet counts alone to determine if the patient needs platelet transfusions and is a useful screening tool for detection of platelet quantitative disorders. Plateletcrit is a measure of the total platelet mass and seems to be more clinically useful than being just an additional value to the laboratory.⁶

Due to alterations in coagulation, the PDW and PCT have an important role in the progression of PE, therefore, not only the platelet count but also the platelet function should be carefully assessed in patients with preeclampsia. There is no conclusive evidence of relationship between these platelet parameters and preeclampsia. Considering the role of the PDW, PCT and platelet indices during the disease as well as the alteration of coagulation, we aimed to compare platelet distribution width and plateletcrit in patients with preeclampsia/eclampsia with healthy controls and to evaluate these indices as potential severity markers of preeclampsia/eclampsia.

METHODS

This is a hospital based observational prospective study conducted in the department of obstetrics and gynecology, S. C. B. Medical College, Cuttack, Odisha during 2017-2019. 400 pregnant women admitted through antenatal clinic and labour room in the 3rd trimester of pregnancy in the department of obstetrics and gynecology, S. C. B. Medical College were taken as study subjects.

A total 400 patients were divided into 2 groups of 200 patients each. The cases and controls groups were matched in gestational age.

- Cases 200 patients with hypertensive disorders of pregnancy.
- Controls 200 healthy pregnant women with blood pressure within normal limits and no proteinuria.

On the basis of blood pressure, urine albumin and convulsions, the cases were divided into 2 groups

- Group 1: preeclampsia patients with BP ≥140/90 mm Hg and urine albumin dipstick screening (1+ or more).
- Group 2: eclampsia patients with BP ≥140/90 mmHg and urine albumin dipstick screening (1+ or more) with convulsions.

For each case selected, a healthy control was matched according to gestational age admitted around the same time during the period of study and followed up. The demographic and clinical data of each participant were recorded in a pre-designed questionnaire. Blood pressure was measured manually using sphygmomanometer. Urine albumin screening was done by dipstick method. All general physical and clinical examinations were done at the hospital to obtain all patient related information. Informed consent was taken from all the patients enrolled in the study.

On admission a complete blood profile of those identified as cases and controls were procured after an oral informed consent. About 2 mL of venous blood samples were collected into K2-EDTA anticoagulant vacutainers and processed in SYSMEX 1000i automated hematology analyzer. All tubes were mixed by inverting the tubes 5-10 times immediately after the blood draw and were sent to the clinical laboratory of Department of Pathology for analysis within 1 hour. All the samples were collected and processed within 4 hours of collection. The results were obtained within 6 hours complying with the pre fixed turn-around time of the department.

All the relevant patient details along with history, clinical examination and hematological evaluation were recorded in a separate spreadsheet and statistical analysis was done.

Inclusion criteria

- Pregnant women between 18-40 years of age
- Women with singleton pregnancies beyond 20 weeks gestation
- For cases, women with pregnancies diagnosed a preeclampsia and eclampsia according to NICE guidelines, 2010
- For controls, healthy women with singleton pregnancies with blood pressure within normal limits and no proteinuria
- Pregnant women admitted to the hospital who gave consent to participate in the study.

Exclusion criteria

- All patients beyond the above-mentioned age groups, patients with gestational hypertension, preeclampsia superimposed on chronic hypertension, essential hypertension, with history of critical illness during pregnancy, prior history of smoking, oral contraceptive use, chronic anticoagulant drug use, or any trauma,
- Patients with gestational diabetes or insulin dependent diabetes mellitus, known cardiac, hepatic or renal disease, HELLP syndrome, asthma requiring steroidal treatment, thalassemia, sickle cell disorder, gestational thrombocytopenia, ITP or other haematological disorders, multifetal gestation or with foetal congenital anomaly, history of molar gestation,

or patients who did not give consent were excluded from the study.

The continuous variables are expressed as the mean \pm standard deviation (SD). Categorical variables were represented using percentages. p value was calculated using Student's t-test and Chi-square test for the continuous and categorical variables respectively. A one-way analysis of variance (ANOVA) was used to compare the participants' platelet indices. Statistical significance was determined using multiple comparisons between the groups performed by one-way ANOVA supplemented with the Scheffe post hoc test. The strength of the association between each of the platelet indices and MAP was estimated using the Pearson correlation coefficient (r). To estimate the sensitivity value as a severity marker of PE, receiver operating characteristic (ROC) analysis was performed.

Statistical analysis

Data was analyzed using Microsoft excel 2016, and IBM SPSS statistics for windows, version 26. A p value ≤ 0.05 was considered significant.

RESULTS

Out of the 200 cases, study had 124 cases with preeclampsia (Group 1) and 76 cases with eclampsia (Group 2), with 200 controls (Group 3).

Table 1: Comparison of baseline characteristics between cases and controls.

Variables	Hypertensives (n=200)	Controls (n=200)	p value
Age (in years)	25.4±4.01	26.7±2.83	0.0004
Primigravida	108	93	0.1336
Low SES	174	171	0.6631
Rural population	174	143	0.0001
<3 ANC	172	127	< 0.00001

Table 2: Comparison of blood pressure in the groups.

Variable	Group 1 (n=124)	Group 2 (n=76)	Group 3 (n=200)	p value
Mean systolic BP (mmHg)	152.7±8.97	160.7±8.97	115.4±6.40	< 0.00001
Mean diastolic BP (mmHg)	103.6±9.68	112.1±9.06	75.9±5.01	< 0.00001

Table 3: Comparison of means of platelet indices in the study groups.

Indices	Groups				
	Preeclampsia (n=124)	Eclampsia (n=76)	Normal (n=200)	p value*	
Platelet count $(10^{3/}/\mu l)$	213.44±43.84 ^a	$178.79 \pm 48.74^{a,b}$	249.72±63.16	< 0.0001	
PDW (fl)	16.84±0.95 ^a	17.64±0.95 ^{a,b}	16.52±0.99	< 0.0001	
Plateletcrit (%)	0.18 ± 0.034^{a}	0.15±0.035 ^{a,b}	0.23±0.048	< 0.0001	

*Statistical significances were tested by one-way ANOVA, ^a p value <0.05 versus normal, ^b p value <0.05 versus preeclampsia.

Most patients in the cases were in the 20-29-year age group 79% with 3.5% below the age of 20 years. 54% patients were primigravida and 86% were unbooked cases with less than 3 antenatal check-ups. Majority of patients belonged to low SES and consisted of rural population (86%).

In the controls, most patients (57%) were in the age group of 25-29 years and there were no patients below the age of 20 years. Almost 47% were primigravida with 64% patients being unbooked. Most patients (86%) belonged to low SES and came from a rural population (72%).

As shown in Table 1, mean age of the cases was 25.4 ± 4.01 years as compared to 26.7 ± 2.83 years in the control group (p=0.0004). There was wider standard deviation in the study group showing that extremes of age was more affected by the disease. In the hypertensive group, majority of patients did not have proper ANCs, with 86% having less than 3 ANCs as opposed to 63.5% in the controls, making it statistically significant (p <0.00001).

Both the cases and the controls were comparable according to the gestational age of the patients, with GA 36.5 ± 3.18 weeks in the hypertensive cases and GA 36.4 ± 2.7 weeks in the controls revealing a statistically insignificant p value (p=0.381).

Table 2 shows significant differences in 'on admission BP' measurements amongst the groups with eclampsia group accounting for the highest.

The modes of delivery were compared among the cases using Chi-square statistics, having a p=0.792 thus showing that there was statistically insignificant difference in the modes of delivery between the 2 groups of patients (p > 0.05).



Figure 1: Distribution of total platelet count (TPC) in cases and controls.

Table 3 shows the comparison between the various platelet indices among the study groups. ANOVA and

post hoc analysis using Scheffe's test was used for comparison. It shows that platelet count was significantly lower in the preeclampsia and eclampsia group compared to the normal subjects. Also, it was found to be significantly lower in the eclampsia group as compared to the preeclampsia group. Platelet distribution width was significantly higher in the eclampsia subjects compared with normal. Plateletcrit also was seen to be significantly lower in preeclampsia and eclampsia subjects compared with the normal, being significantly lower in the eclampsia group.

Boxplot graph showing distribution of platelet count in the 3 groups is shown in Figure 1. Group 1 has a range of $211 \times 103/\mu$ 1 with a minimum of $100 \times 103/\mu$ 1 and maximum of $311 \times 103/\mu$ 1. The median value was $204 \times 103/\mu$ 1. The 25th quartile is $187.25 \times 103/\mu$ 1 with 75th quartile being 245.75 \times 103/\mu1. Group 2 has a range of $219 \times 103/\mu$ 1 with a minimum of $106 \times 103/\mu$ 1 and maximum of $325 \times 103/\mu$ 1. The median value was $164 \times 103/\mu$ 1. The 25th quartile is $132.25 \times 103/\mu$ 1 with 75th quartile being $195 \times 103/\mu$ 1. Group 3 has a range of $253.7 \times 103/\mu$ 1 with a minimum of $111 \times 103/\mu$ 1 and maximum of $392.4 \times 103/\mu$ 1. The median value was $253.7 \times 103/\mu$ 1. The 25th quartile is $198.8 \times \times 103/\mu$ 1 with 75^{th} quartile being $297.97 \times 103/\mu$ 1.



Figure 2: Distribution of platelet distribution width (PDW) in cases and controls.





In Figure 2, the boxplot graph shows distribution of platelet distribution width in the 3 groups. Group 1 has a range of 5.2fl with a minimum of 14.3fl and maximum of 19.5fl. The median value was 16.9fl. The 25^{th} quartile is 16.3fl with 75th quartile being 17.3fl. Group 2 has a range of 5.5fl with a minimum of 13.8fl and maximum of 19.3fl. The median value was 17.75fl. The 25^{th} quartile is 17.4fl with 75^{th} quartile being 18.2fl. Group 3 has a range of 5.9fl with a minimum of 12.9fl and maximum of 18.8fl. The median value was 16.6fl. The 25^{th} quartile is 15.82fl with 75^{th} quartile being 17.2fl.

Figure 3 is boxplot graph showing distribution of plateletcrit in the 3 groups. Group 1 has a range of 0.15% with a minimum of 0.12% and maximum of 0.27%. The median value was 0.18%. The 25^{th} quartile is 0.16% with 75th quartile being 0.21%. Group 2 has a range of 0.16% with a minimum of 0.12% and maximum of 0.28%. The median value was 0.14%. The 25^{th} quartile is 0.13% with 75th quartile being 0.17%. Group 3 has a range of 0.2% with a minimum of 0.15% and maximum of 0.35%. The median value was 0.23%. The 25^{th} quartile is 0.19% with 75th quartile being 0.27%.



Correlation between MAP (in mmHg) and platelet count with the Pearson's correlation coefficient r= -0.45 with p <0.0001 in a 2-tailed analysis.

Figure 4: Scatter diagram of total platelet count and mean arterial pressure in the hypertensive group.



Correlation between MAP (in mmHg) and platelet distribution width (PDW in fl) with the Pearson's correlation coefficient r= 0.97 with p <0.0001 in a 2-tailed analysis.

Figure 5: Scatter diagram of platelet distribution width by mean arterial pressure in the hypertensive group.

Pearson's correlation coefficient was calculated for platelet indices with respect to mean arterial pressure. Platelet count and plateletcrit showed a negative correlation with MAP whereas platelet distribution width showed a maximum positive correlation. All the correlation coefficients were statistically significant. These correlations are shown in Figures 4-6.



Correlation between MAP (in mmHg) and plateletcrit (PCT in %) with the Pearson's correlation coefficient r= -0.45 with p <0.0001 in a 2-tailed analysis.

Figure 6: Scatter diagram of plateletcrit by mean arterial pressure in the hypertensive group.



Figure 7: The ROC curve of platelet indices in the preeclampsia group to identify the optimal cut-off levels for the prediction of severity of the disease.



Figure 8: The ROC curve of platelet indices in the eclampsia group to identify the optimal cut-off levels for the prediction of severity of the disease.

As seen in Table 4, for preeclampsia group, women with TPC $<222.05\times103/\mu$ l were at high risk of developing severe disease with a sensitivity of 66.5% and specificity of 64.5%. The AUC was 0.67 which shows not so good predictability for the severity of the disease. Women with PDW <16.85fl were at risk for developing a severe

disease with a sensitivity of 62% and specificity of 51.5%. The AUC 0.58 which shows a poor predictability. Women with PCT <0.22% were at risk of developing severe disease with a sensitivity of 53.5% and a high specificity of 85.5%. The AUC of 0.75 shows that it has a good predictability.

Groups	Parameters	Sensitivity (%)	Specificity (%)	Cut-offs	AUC	95%CI AUC	Significance
Preeclampsia	TPC (10 ³ /µl)	66.5%	64.5%	222.05	0.67	0.61-0.73	< 0.0001
	PDW (fl)	62.0%	51.5%	16.85	0.58	0.52-0.64	0.01
	PCT (%)	53.5%	85.5%	0.22	0.75	0.70-0.80	< 0.0001
Eclampsia	TPC (10 ³ /µl)	83.5%	73.7%	186.55	0.83	0.77-0.88	< 0.0001
	PDW (fl)	79.0%	76.3%	17.35	0.80	0.13-0.25	< 0.0001
	PCT (%)	89.5%	73.7%	0.16	0.90	0.85-0.94	< 0.0001

For eclampsia group, women with TPC $<186.55 \times 103/\mu$ l were at high risk of developing a severe form of the disease with a sensitivity of 83.5% and specificity of 73.7%. The AUC was 0.83 which it has a fairly good predictability of detecting severity. Women with PDW <17.35fl were a risk of developing severe disease with a sensitivity of 79% and specificity of 76.3%. The AUC was 0.8 shows a fairly good predictability. Women with PCT <0.16% had a risk of developing severe disease with a sensitivity of 89.5% and specificity of 73.7%. The AUC 0.9 shows PCT to be a good predictor for assessing severity of eclampsia.

DISCUSSION

Preeclampsia/eclampsia remains one of the causes of perinatal mortality and maternal death in most developing countries. Many theories suggested that placental change is one of the critical issues in the pathogenesis of preeclampsia.⁷ Its diagnosis is made primarily based on blood pressure measurement, determination of the proteinuria and clinical data.

There was no statistically significant difference between the groups according to parity and socioeconomic status. Both the groups had primigravida and patients from low SES as the majority. The majority of study group (87%) belonged to a rural population as compared to the controls (71.5%) as maximum patients in the study group were referred cases from peripheral setups (p <0.05).

Also, there was a statistically significant difference in the groups (p < 0.00001) according to the number of ANCs received, showing that with better antenatal care, early identification and proper management of high risks groups may be possible. Yang et al, showed a statistically significant difference in baseline characteristics between healthy controls and preeclampsia group in their study with respect to nulliparity, BMI, age of subjects, gestational age and birth weight of babies post-delivery.⁸

Mean birth weight of babies in the preeclampsia group 1.9 ± 0.47 kg and 2.3 ± 0.45 kg in the eclampsia group showing a statistically significant difference (p <0.0001) on comparing the birth weights. This may be explained by the fact that most subjects in the eclampsia group were referred as term patients in labour whereas in the preeclampsia group most subjects were referred as preterm patients with high BP and the decision of delivery was taken due to maternal indications.

Buchbinder et al, concluded that in women who have gestational hypertension or preeclampsia, increased rates of preterm delivery and delivery of small-for-gestationalage infants are present only in those with severe hypertension. In these women, the presence of proteinuria does not influence perinatal outcome.⁹

In the present study, there was a statistically significant decrease in the platelet counts and plateletcrit values between the study subjects and the controls, and a rise in the platelet distribution width (p < 0.0001). Among the preeclampsia and the eclampsia subjects also there was a statistically significant difference as evaluated using ANOVA and post hoc analysis. Thus, these indices were associated with disease severity. Several other studies have shown similar results.

Sheeha A et al, demonstrated significantly lower PC and PC to MPV ratio in patients with preeclampsia compared with the normal controls but failed to show similar trend when MPV and PDW were evaluated in the same study groups.¹⁰

Doğan et al observed significantly lower PC and PC/MPV in preeclamptic women compared with the controls. The same study documented significantly higher MPV in preeclamptic women than the control group. However, they found no significant difference in PDW among women with severe preeclampsia, mild preeclampsia, and healthy controls.¹¹

Likewise, Freitas et al, reported lower PC in women with preeclampsia.¹²

Giles examined the association between PC and MPV in 5000 pregnant women in early pregnancy and observed that normal PC and increased MPV were associated to PE occurrence.¹³

Dadhich et al, also found decreased platelet count in patients with PE compared to normal pregnancy.¹⁴

In this study subjects, we found a strong positive correlation of PDW with mean arterial pressure having Pearson's coefficient of 0.97 which was statistically significant (p <0.0001). As mean arterial pressure is directly related to the severity of the disease, we can say that platelet indices especially PDW is related to the severity of preeclampsia.

Yang et al also demonstrated that in pregnant women with PE, the platelet count and PCT had a negative correlation with the mean arterial pressure (MAP), whereas the MPV and the PDW showed a positive correlation with the MAP. Among the evaluated platelet indices, they observed only the PDW to have a statistically significant correlation with the MAP, which they demonstrated to be the best-known severity marker of PE.⁸

ROC curves along with Youden's index were used to derive diagnostic cut-offs for platelet indices in both the preeclampsia and eclampsia group. For the preeclampsia group, we found PCT to be a fairly good predictor to assess the severity of the disease. Same was found for the eclampsia group. Along with PCT, PDW was found to be a good predictor for eclampsia group. This shows an accelerating replacement of the platelets by the bone marrow in severe preeclamptic women resulting in platelet anisocytosis, based on PDW values. PCT was significantly decreased, which reflects platelet count reduction as seen with increasing severity of disease.

Yang et al, demonstrated in their study, that although all participants had a normal platelet count, it gradually decreased below the normal range as the PE progressed. The PDW, however, increased significantly above the normal range. These results revealed the continuous platelet consumption during PE progression as well as the activation of platelets that compensate for the decrease in the platelet count. Therefore, the PDW was proposed to play a role as a prediction marker for the severity of PE before the low platelet counts are observed. In addition, it can be used to predict abnormal uncontrolled platelet activation before the progression from PE to severe PE with complete HELLP.⁸

Freitas et al, found that PCT was levels were lower in severely preeclamptic subjects as compared to healthy non pregnant controls.¹² Their study only included women with severe preeclampsia. However, we evaluated

preeclampsia and eclampsia patients together. Low levels of PCT in this study reflect platelet effect rather than MPV, as PCT is the product of platelet count and MPV.

A limitation of this study was the lack of serial detection of the platelet indices through the complete pregnancy period. The time when the platelet indices especially PDW and PCT increases during pregnancy will need further evaluation. Within this study, however, the results are useful for predicting the progression of severe PE. Furthermore, the results can be used to help decide on the timing of delivery for women with PE. In addition, the platelet indices have slightly different normal ranges, as determined by the different laboratory machines used for analysis. Therefore, it is necessary to adjust the data to allow for these differences in the normal ranges, as determined by different machines.

In recent studies, the platelet indices are newly assessed in terms of thrombocytosis, respiratory disease, and heart disease.¹⁵⁻¹⁷ Study data suggest new aspects for the use of the same in obstetrics as useful clinical marker.

CONCLUSION

Currently, one the most important goals in obstetrics is the identification of pregnant with an increased PE risk. Besides, the definition of sensitive and specific biomarkers would allow not only the detection of patients at risk of PE, but it would also allow a close surveillance, a precise PE diagnosis and a timely pregnancy intervention. In this context, platelet indices emerge as a good candidate, since it is a simple and habitually done method, with lower cost and greater accessibility in the clinical laboratory. It is known that severe PE is associated with platelet activation and significant haemostatic abnormalities, which result in serious complications for the mother and new-born.

This study suggests that platelet distribution width and plateletcrit are useful in risk evaluation of preeclampsia. These a valid measurement tool to predict the severe progression of PE even when normal platelet counts are observed. Both these indices show a definite correlation with rising diastolic pressures. Plateletcrit has a good predictability as a severity marker in patients with eclampsia, though both these indices have some predictive power in assessing the severity of hypertensive disorder of pregnancy. Further large-scale prospective studies are required to reach to a definitive conclusion.

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