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The Value of Platelet Volume Parameters and Procalcitonin in the Diagnosis of Neonatal Sepsis

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ABSTRACT

Background: In developing countries, sepsis represents the 3rd cause of neonatal mortality. Procalcitonin and MPV have been studied widely as markers for neonatal sepsis.
Aim of The Work: To evaluate the value of platelet volume parameters compared to procalcitonin as early biomarkers of neonatal sepsis.
Patient and Methods: a prospective case-control study conducted on 80 newborn infants admitted to the university neonatal intensive care unit, Sayed Galal University Hospital, between September and December 2020. Studied neonates have been divided equally into; sepsis, and control groups. Cases were suspected based on clinical presentation, risk factors, and hematological scoring system (≥3); and further subdivided into group A: with proven sepsis, and group B: with clinical sepsis. Serum procalcitonin, CRP, blood cultures, and CBC were performed within the 1st 36 hours of life.
Results: MPV was higher in both sepsis (p<0.0001), and culture-proven sepsis groups (p=0.00057). Other platelet parameters showed no significant difference among sepsis and control groups. Procalcitonin level was higher in both sepsis (p< 0.00001), and culture-proven sepsis groups (p< 0.00001). MPV of ≥ 9.54 fL, and PCT of ≥ 0.157 ng/mL cutoff points showed sensitivity, specificity, PPV, and NPV of (92.5%, 87.5%, 88.1%, 92.1%) respectively for MPV, and (95%, 65%, 73.1%, 92.9%) respectively for PCT. MPV showed also positive correlation in sepsis group (p= 0.02089, 0.03134) with PCT and CRP respectively.
Conclusion: MPV and PCT showed close sensitivities, while MPV septicity was even higher. MPV may be considered as a sensitive, affordable, and reliable marker for neonatal sepsis.

Keywords: *Sepsis; Neonate; Procalcitonin; Platelets.*

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INTRODUCTION

Neonatal sepsis is responsible for about 13% of all neonatal mortalities and 42% of deaths during the period from 1-7 days after birth.[1] It could be classified as early-onset and late-onset according to the age of the newborn at the onset of the sepsis episode.[2] Researchers have discovered several biomarkers that help us to diagnose and manage sepsis as early as possible.[3] Procalcitonin (PCT) can differentiate sepsis from healthy control neonates even better than CRP.[4] The mean volume of platelets is a sensitive and cost-effective marker for neonatal sepsis.[6]

PATIENTS AND METHODS

This study was conducted between September and December 2020, on 80 newborn infants admitted to the university neonatal intensive care unit, Sayed Galal University Hospital during the period of the study.

Included neonates were 2 groups: Control group (40 neonates) who were healthy, full-term neonates with birth-weight >2500 grams. Case group (40 neonates) with neonatal sepsis suspected based on the presence of ≥1 of the following: Clinical signs and symptoms suggesting sepsis such as a poor feeding, lethargy, irritability, respiratory distress, hypotension, and poor perfusion. Laboratory heamtological scoring system of ≥3. History of maternal risk factors such as a chorioamnionitis and PROM (≥18 h), or fetal risk factors such as a prematurity and low birth weight. Case group was further subdivided according to the culture results into: Culture-positive (confirmed) sepsis subgroup (15 neonates), and Culture-negative (clinical) sepsis subgroup (25 neonates). Viral neonatal sepsis due to possible Covid-19 pandemic infection was excluded by excluding infants of Covid-19 PCR positive mothers and infants of suspected mothers based on clinical or radiographic data. Preterm neonates < 34 weeks gestation, newborns with multiple congenital anomalies, intracranial hemorrhage, or suspected to have inborn

errors of metabolism were also excluded from our study. Gestational age was determined by Ballard score.[7]

Included neonates were subjected to: Full perinatal and family histories. Serial physical examinations since the onset of sepsis. Laboratory investigations: Complete blood count (CBC) done by CELL-DYN 3200 Systems, Serum level of C-reactive protein done by Latex agglutination technique, and serum level of procalcitonin done by ELISA open-system. Blood sampling (≥1 CC) was performed for blood culture. Lumbar puncture was done only for neonates with neurological symptoms such as a seizures. Chest radiograph was done only for neonates with respiratory presentations such as a tachypnea. Echocardiography was done only for neonates with cardiac presentations such as a murmur. CBC and serum Procalcitonin were performed for all included neonates during the 1st 36 hours of life, and within 12 hours from the onset of the sepsis episode in sepsis group. Hematological scoring system[5] was calculated for all included cases. (Table 1)

Test	Abnormality	Score
Total WBC count	≤ 5 x 10^3.	1
	≥ 25 x 10^3 at the 1st hour of life, ≥ 30 x 10^3 at 12–24 hours, or ≥ 21 x 10^3 at ≥ 24 hours of life.	1
Total PMN count	No any mature PMN.	2
	Decreased (≤ 1800), or Increased ≥ 5400 at birth, 14x10^3 at 12-48 hours, or 5400 at ≥ 48 hours of life.	1
Immature PMN count	Increased (> 600).	1
Immature/ Total ratio	Increased (> 0.120).	1
Immature/ Mature ratio	0.3, or more.	1
Degenerative PMN	Cytoplasmic vacuoles, or ≥3 toxic granules.	1
Platelet Count	≤ 150 x 10^3.	1

Table 1: WBC: White blood cells, PMN: Polymorphonuclear cells. Cell count is in Cell /mm3.

A score of 2 or less was interpreted as mostly no sepsis, score of 3-4 was a possible sepsis, and score of 5 or more was considered as very likely to have sepsis.

Data was analyzed using IBM SPSS software package 25.0. (NY: IBM). Kolmogorov-Smirnov test verified the normality of the distribution. Descriptive statistics were given. Chi-square test was used to compare different groups for categorical data, and Fisher's exact test was used for the correction of chi-square results if > 20% of the cells have a count <5. We compared parametric quantitative variables between 2 groups using T-test, and ANOVA one-way test has been used if there were > 2 groups. We also used the Mann-Whitney test to compare non-parametric quantitative variables of 2 groups, while the Kurskal-Wallis test was used when there were > 2 groups. For correlation between 2 variables we used Spearman's correlation coefficient test.

RESULTS

This study was conducted between September and December 2020, on 80 newborn infants admitted to the NICU, Sayed Galal University Hospital.

In our study, we couldn't find any significant difference between sepsis and control groups as regards sex. However, there was a significant difference as regards gestational age, mode of delivery, birth-weight, NICU admission duration, and PROM duration. (Table 2)

	Sepsis neonates (no.= 40)		Control neonates (no.= 40)		P-Value
	No.	%	No.	%	
Male	22	55	21	52.5	0.6604
Female	18	45	19	47.5	
Full-term	8	20	40	100	< 0.00001*
Pre-term	32	80	0	0	
CS	32	80	22	55	0.0091*
NVD	5	12.5	17	42.5	
SVD	3	7.5	1	2.5	
Maternal morbidity	26	65	8	20	1
Mortality	3	7.5	0	0	
Birth-weight (grams)	**1686.18 ± 656.676**		**2643.25 ± 122.336**		< 0.0001*
PROM (hours)	**22.525 ± 14.823**		**7.025 ± 6.082**		< 0.00001*

Table 2: CS: cesarean section, SVD and NVD: spontaneous and normal vaginal deliveries, NICU: neonatal intensive care unit, PROM: premature rupture of membranes. *: significant at p ≤ 0.05.

In our study, a significant difference among sepsis and control groups was found as regards MPV and PCT. However, there was no significant difference as regards other platelet indices. (Table 3)

	Sepsis (no.=40) Mean±SD	Control (no.=40) Mean±SD	P-value
MPV	**10.542 ± 0.965**	**8.648 ± 0.734**	**< 0.0001***
PC	**144.94 ± 45.72**	**166.21 ± 64.59**	**0.0935**
Plct	**0.15 ± 0.044**	**0.143 ± 0.057**	**0.499**
PDW	**18.09 ± 2.925**	**17.50 ± 1.20**	**0.242**
PCT	**0.302 ± 0.190**	**0.144 ± 0.031**	**< 0.00001***

Table 3: MPV: mean platelet volume. PC: platelet count. Plct: plateletcrit. PDW: platelet distribution width. PCT: Procalcitonin.

In our study, a significant difference among all groups was found as regards MPV and PCT level. However, there was no significant difference as regards other platelet indices. (Table 4)

	Proven sepsis (n=15) Mean±SD	Clinical sepsis (n=25) Mean±SD	Control (n=40) Mean±SD	P-value
MPV	**9.962 ± 0.6432**	**10.889 ± 0.9678**	**8.648 ± 0.734**	**< 0.00001***
PC	**162.20 ± 48.20**	**134.58 ± 41.75**	**166.21 ± 64.6**	**0.0784**
Plct	**0.16 ± 0.046**	**0.145 ± 0.043**	**0.143 ± 0.057**	**0.550**
PDW	**17.936 ± 0.966**	**18.192 ± 3.65**	**17.50 ± 1.20**	**0.474**
PCT	**0.185 ± 0.014**	**0.373 ± 0.212**	**0.144 ± 0.031**	**< 0.00001***

Table 4:

In our study, only MPV showed a significant correlation with PCT level. (Table 5)

	Sepsis (PCT) (n=40)		Control (PCT) (n=40)	
	Rho	P-value	Rho	P-value
MPV	**0.36414**	**0.02089***	**0.10452**	**0.52097**
Plct	**-0.1698**	**0.29489**	**0.00382**	**0.98135**
PDW	**0.06464**	**0.69191**	**0.15377**	**0.34348**
PC	**-0.25959**	**0.10575**	**-0.04662**	**0.77512**

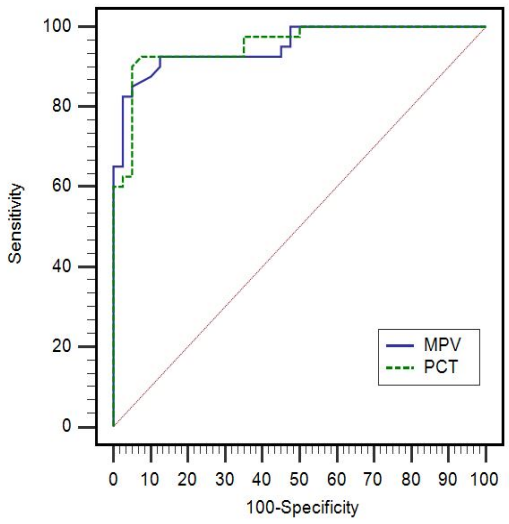
Table 5: Rho: Spearman's correlation test.

In our study, MPV in sepsis groups showed a significant correlation with CRP level. In contrast, correlation between HSS and MPV in the sepsis group was not statistically significant. (Table 6)

	Sepsis (MPV) (n=40)	
	Rho	**P-value**
HSS	**0.0164**	**0.919995**
CRP	**0.34092**	**0.03134***

Table 6: HSS = Hematologic scoring system. CRP = C-reactive protein.

Comparing ROC curves for both MPV and PCT, we found that MPV sensitivity approaches that of PCT with even higher specificity in sepsis cases.(Figure 1)



Test	AUC	SE	95 CI		cutoff	Sensitivity	Specificity	+PV	-PV
			Lower	Upper					
PCT	**0.954**	**0.0217**	**0.0882**	**0.988**	**≥ 0.157**	**95**	**65**	**73.1**	**92.9**
MPV	**0.952**	**0.0224**	**0.879**	**0.987**	**≥ 9.54**	**92.5**	**87.5**	**88.1**	**92.1**

Fig. 1: AUC: Area under curve. SE: Standard error of the AUC. CI: Confidence Intervals. +PV and -PV: Positive and negative predictive values

DISCUSSION

Many researchers have been looking for new markers for neonatal sepsis for several years. In our study, we were looking for a sensitive, cost-effective, and reliable marker that may help us to make the decision of starting antibiotic therapy for bacterial neonatal sepsis. MPV is a sensitive and cost-effective marker of neonatal sepsis.[6]

Included neonates were subjected to the following: Full perinatal and family histories. Serial physical examinations since the onset of sepsis. Laboratory investigations. CBC and serum Procalcitonin were performed for all included neonates during the 1st 36 hours of life, and within 12 hours from the onset of the sepsis in sepsis group.

In our study, as regards the demographic data, there were 43 male neonates [22 (55%) case, and 21 (52.5%) control], and 37 female neonates [18 (45%) case, and 19 (47.5%) control]. Birth-weight Mean±SD was 1686 ± 656.67 grams for the case group, and 2643 ± 122.33 grams for the control group. Regarding gestational age, neonates were classified as 48 Full-term [8 (20%) case, and 40 (100%) control], and 32 preterm, all preterm neonates were in the case group (as 80%). Gestational age was determined by Ballard score.[7]

As regards both gestational age and birth-weight, a significant difference between sepsis and healthy neonates was found (P-value of <0.00001, and <0.0001 respectively) with a higher prevalence of sepsis in preterm, as well as in LBW neonates. This in accordance with Belachew & Tewabe, who reported that sepsis incidence was higher with both prematurity and low birthweight.[8]

In our study, regarding the mode of delivery, sepsis was more prevalent with cesarean section (p-value= 0.009). CS represented 80% of neonates in sepsis groups (n = 32), and 55% in control group (n= 22). The percentage of births by CS 2007-2014 in Egypt was 52%.[9]

In our study, PROM ≥ 18 hr represented a major risk factor for sepsis (p-value <0.00001) in 30 cases (75%). This is in accordance with Atrolia et al. who reported that PROM is a leading cause of prematurity and neonatal sepsis.[10]

Regarding platelet parameters, according to Go et al., the normal ranges were: PC: 150 – 450 × 10^9/L; MPV: 7.4 - 10.4 fL; PDW: 8.3 - 56.6 %; PCT: 0.22-0.24%. Go et al. has conducted a large cohort study that showed no differences in platelet volume parameters at birth between late-preterm and term neonates.[11] However, previous report by Alicja et al. indicated that platelet count and plateletcrit were lower in late-preterm neonates compared with term neonates.[12]

In our study, Regarding MPV, it was significantly higher in sepsis group than in control group (P-value <0.0001). It was also significantly higher in proven sepsis than in other groups (p-value = 0.00057). So an MPV value of ≥ 9.54 fL may be considered as a good marker for sepsis. This is in accordance with Hanaganahalli et al.[6] We noticed that this value was normal for age and may be insignificant alone. Small sample in our study could be the reason.

As regards other platelet indices, we found no significant difference among sepsis and healthy groups with p-values of (0.499, 0.242, and 0.093) respectively. They also showed the same results for proven sepsis, clinical sepsis, and control groups with p-values of (0.550, 0.474, and 0.078) for Plct, PDW, and PC respectively.

This is in accordance with Hanaganahalli et al. as regards PDW, but against their results regarding PC and Plct. Hanaganahalli et al. reported that platelet count and plateletcrit were increased in proven sepsis group more than in clinical sepsis and control groups. [6] We suggest that this is due to the low number of cases in our study and the measurement timing during the early phase of sepsis.

Tayman et al. reported that, in sepsis, PC was observed to decrease while MPV was observed to increase in consecutive measurements. These results were against our results as regards PC which may be explained by their serial measurements against our single measurement. Time allows platelet parameters to be affected during the sepsis process, and this can only be noticed with serial measurements.[13]

As regards normal serum procalcitonin (PCT), Naramura et al. reported that, gestational age (GA) had no significant effect on serum procalcitonin levels during the 1st 48 hours of life. In contrast, Fukuzumi et al. reported that the median level of PCT at day 1 was lower in term and preterm infants than in other preterm neonates. [13, 14]

According to Naramura et al., PCT levels at 12–36 hours of life were 0.14–4.39 ng/mL and 0.15–4.44 ng/mL in term and preterm neonates respectively. These values were < half Fukuzumi et al. results. Naramura et al. excluded the cases of respiratory failure, which causes a rise in PCT level unlike Fukuzumi et al. [13, 14] In our study, we included only late-preterm and term neonates and relayed on Naramura et al. results.

In our study, serum PCT levels in sepsis group were higher than in control group (p-value < 0.00001). It was also higher in proven than in clinical sepsis and control groups (p-value < 0.00001). So the cutoff level of PCT of ≥ 0.157 ng/mL may be considered as a good marker for neonatal sepsis. This is in accordance with Umran et al. and Aydemir et al. [15, 16]

In our study, we found positive correlations between MPV and both PCT level and CRP level in sepsis group. This is in accordance with Tayman et al as regards CRP. We could not find any previous correlation between PCT and MPV.[12]

After comparing the two ROC curves for both MPV and PCT, we found that MPV sensitivity approaches that of PCT with even higher specificity in sepsis cases. Both of them increased in the first few hours from the sepsis onset.

Our aim was to find an ideal screening marker for neonatal sepsis cases in order to minimize the complications of both sepsis and empiric antibiotic treatment.

The ideal screening marker for sepsis would be highly sensitive (to allow early diagnosis), highly specific (to allow appropriate treatment), of low cost (to be affordable), and easily performed (requires a small sample and an easy technique). In our study, many of these criteria were found in both PCT and MPV. MPV was more easily performed, had a lower cost, and a higher specificity for sepsis. However, as the cutoff level of MPV in our study was found to be within the normal range, we suggest it to be added to other screening markers.

Our study had some limitations including: the low number of cases and the single measurement method. We did not choose to do serial measurements due to the high cost and the inappropriate results for the aim, as our aim was to measure the level of PCT and platelet parameters during the early phase of the sepsis process. We thought that serial measurements are useful for prognostic not screening targets, and in that matter, CRP is a very effective marker with a low cost and simple measurement techniques.

CONCLUSION

The significant results among the studied groups were for both mean platelet volume (MPV), and Procalcitonin (PCT). With close sensitivity in both and a higher specificity of MPV. The cutoff value of ≥ 9.54 fL MPV and of ≥ 0.157 ng/mL serum PCT level were considered to have a diagnostic significance in sepsis. However neither one of them

can be used as a diagnostic marker alone as their cutoff levels are in the normal range for age.

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