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Serum Urate and Some Platelet Studies in Neonatal Sepsis

Ashraf Mohamed Abdel Fadil[3*], Kamel MM[1], Osman KS[2], Mosa FA[4]

[1]Pediatric Department, Faculty of Medicine, Minia University, Egypt.

[2]Clinical Pathology Department, Faculty of Medicine, Minia University, Egypt.

[3*]Faculty of Medicine, Minia University, Egypt.

[4]Dermawas Hospital, Egypt.

[*]**Corresponding author:** Ashraf Mohamed Abdel Fadil, Faculty of Medicine, Minia University, 521, 20th Street, Bolak El Dakror, Giza, Po-12987, Egypt, Tel: 00201068445424, E-mail: ashraf1191@yahoo.com

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Abstract

Background: Mean Platelet Volume (MPV) that is included in blood tests as part of the CBC, will be larger with platelet destruction problems as with NS or when the body is producing increased numbers of platelets. Neonatal Sepsis (NS) is also associated with increased production of reactive oxygen species that will lead to consumption of specific antioxidant molecules like uric acid.

Objective: Aimed to determine the role of MPV and uric acid levels in the diagnosis ofNS.

Methods: This study had been carried out in NICUs of El-Minia University Hospital and Dermawas central hospital between September 2014 and March 2015. A total of 70 newborns involved in this study, the neonates were divided in to three groups: Group I (n=50): clinical NS, Group II (n=50): culture proven NS, Group III (n=40): healthy controls. Hemoglobin level, hematocrit value, platelet count, mean platelet volume, leucocytic count, C reactive protein, ANC (absolute neutrophilic count) and uric acid levels were done to all newborns, blood cultures were done also.

Results: Patients in Group II had the highest C-Reactive Protein (CRP) levels (71.5±124.3 mg/L), lowest platelet counts (171.5±45/mm3) and lowest uric acid levels ((1.9±0.9mg/dl) when compared to Groups I and III ($p<0.05$), for all comparisons). MPV values were higher in Group I (11.7±1.3fL) and Group II (12.2±2.5fL) when compared to Group III (8.5±0.5fL) ($p=0.001$), although there was no difference between Groups I and II. Area under curve values for CRP, MPV, and uric acid were 0.92 ($p=0.001$), 0.76 ($p=0.001$) and 0.28 ($p=0.001$), respectively. The diagnostic cutoff values for CRP and MPV were 9.5 mg/dL and 10.4 fl respectively. Sensitivity and specificity of MPV in NS were 100% and 100% respectively. When combined with CRP its sensitivity and specificity is 96% and 100 % respectively.

Conclusions: The combined use of CRP and MPV should be considered in the early diagnosis of NS, but uric acid levels may only be utilized as an additional tool to support diagnosis. MPV is shown to be more sensitive and specific than CRP and uric acid in diagnosing neonatal sepsis.

Keywords: MeanPlateletVolume;Neonatal Sepsis; Thrombocytopenia; Uric Acid

Background

Neonatal sepsis still one of the leading causes of morbidity and mortality in both term and preterm infants [1]. Clinically suspected sepsis" is one of the commonest diagnoses in NICU [2], because the symptoms and signs of neonatal sepsis are nonspecific and are observed with inflammatory syndromes of noninfectious origin that mimic those of neonatal sepsis [3].

So, identifying neonates with a high clinical suspicion of sepsis rapidly and initiating antimicrobial therapy still remain the most important challenge for clinicians. Thrombocytopenia due to platelet destruction is an early laboratory sign of NS but also, non-specific sign [4-6]. Moreover, clinical response to antimicrobial therapy cannot be judged by platelet counts which remain depressed for days to weeks after sepsis [7].

MPV is higher with platelets destruction as is seen in immune thrombocytopenic purpura (ITP) and inflammatory bowel diseases [8]. NS is also associated with excessive production of reactive oxygen species that consume body antioxidant activity; therefore, low blood levels of specific antioxidant molecules like uric acid can provide evidence of oxidative stress of sepsis [9]. However,while much is known about neonatal sepsis, MPV & antioxidant activity is not well studied.

Aim of the Work

To determine the role of Mean Platelet Volume (MPV) and uric acid levels in the diagnosis of Neonatal sepsis.

Methods

This case-control study had been carried out in NICU of El-Minia University Hospital and Dermawas central hospital between September 2014 and March 2015. Patients enrolled in the study are newborns either full term or preterm, from both sexes, with clinical symptoms and signs of sepsis within 1st month of life, laboratory data showing sepsis (leukocytosis or leukopenia, elevated immature to total neutrophil ratio, thrombocytopenia and increased CRP ± +Ve blood culture. Patients excluded from the study are Newborns undergoing a course of antibiotics prior to blood sampling, newborns undergoing surgery in the previous week, chromosomal abnormality, lack of consent from the parents, Inadequate sampling for all tests.The subjects were classified into one of the following three groups: Group I (n=50): clinical NS; Group II (n=50): culture proven NS; Group III (n=40): healthy control.

The patients included in Group I if they had two or more clinical findings: either respiratory dysfunction (tachypnea with respiratory rate >60 breaths/min, intercostal or sub costal retractions, apnea, or central cyanosis); or circulatory dysfunction (poor peripheral circulation, hypotension, tachycardia, shock and prolonged capillary refill >3 seconds); or GIT dysfunction (abdominal distension, bloody stool, feeding intolerance, hepatomegaly and jaundice; neurological dysfunction (irritability, convulsion, hypotonia and lethargy; hematological dysfunction (bleeding tendency); renal dysfunction: oliguria, unstable temperature (<36.5°C or >37.5°C on two occasions within 12 h). with additional laboratory findings [leukocytosis (>20,000/mm3) or leucopenia (<5,000/mm3); immature/total neutrophil count >0.2; thrombocytopenia (<150,000/mm3)], but culture negative.

Group II was culture proven neonatal sepsis; and forty sex, gestational age, birth weight, mode of delivery and five minute Apgar score matched healthy stable control enrolled in this study. They were born to healthy mothers with negative medical and obstetric history and considered as Group III.

Complete blood count with differential leucocytic count and platelet counts were measured at time of sepsis evaluation. The sample was 2 mL of fresh venous blood which collected from peripheral veins of neonates by sterile venipuncture and put in a sterile vacutainer tube containing K2 EDTA as anticoagulant, complete blood counts were performed electronically. Immature neutrophil count was determined by multiplying the percentage of bands, metamyelocyte and myelocytes by the absolute neutrophil count. Immature to total neutrophil ratio (I/T) was calculated as: (Bands + metamyelocyte + myelocytes)/ (segmented neutrophil + bands + metamyelocyte + myelocytes). Shift to left is defined when ratio is 0.2 or more. Thrombocytopenia is considered if less than 150000/mm3. Leukocytosis and leukopenia are defined as more than 20,000/mm3and fewer than 5000/mm3, respectively. Platelet count and MPV were determined using a Beckman Coulter hematology analyzer. Serum CRP levels were measured by nephelometry. Serum uric acid levels were detected using the spectrophotometric method. Serum concentrations of CRP were measured by a Tinaquant CRP(Latex) high sensitive immunoturbidimetric assay on the Roche Modular P analyzer according to the manufacturer's instructions (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, D-68298, Mannheim, Germany). CRP was considered high if the value exceeded 4.05 mg/L(Dilli D, OğuzŞS, Dilmen 2010). Blood cultures were performed on infants when NS was suspected. The Bactec microbial detection system (BACTEC™ 9120) (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) was used to detect positive blood cultures.

C-Reactive Protein (CRP) quantitative assay

Sample collection and preparation- Serum samples were used (1 mL blood was put in a sterile plain vacutainer tube and let to clot naturally then serum was separated for CRP measurement). Samples were separated as soon as possible to prevent hemolysis. Sera may be stored at 2-8◦C for 48 hours, otherwise samples were freezed at -20◦C or below; we did not freeze and thaw sera more than once. Sample dilutions were freshly prepared on the day of assay. N.B.Turbid and hemolyzed samples are not suitable for nephelometric assays.

Test principle

Particle-enhanced immunonephelometry is applied. This method involves measuring the light scattered by insoluble complexes formed by reaction between specific protein in samples and its respective antibody covalently coupled to latex particles, and the amount of scattered light is directly proportional to the concentration of the protein under condition that antiserum is in excess.

The latex particles increase the size of complexes formed and thus the amount of light as well as the test sensitivity. Concentrations are automatically calculated by reference to a calibration curve stored in the instrument.

The study was carried out according to the principles of declarations of Helsinki, and its appendices [10] and was approved the hospital ethical review board in El Minia university hospital (code 75a, March 2015). Written informed consents from patients' caregivers were obtained for the use of their study-related information and for participation in the ongoing research.

Results

Table 1 and Table 2 Comparison between case (Group I & II) and control groups according to Demographic data:No statistical differences were detected among the 3 groups with respect to demographic data including type of delivery, gender, gestational age, birth weight and rate of prematurity as demonstrated in Table 1 and Table 2. However, the postnatal hospitalization age was greater in the sepsis groups than that of the controls as shown in Table 3.

Table 4 frequency of clinical criteria indicating sepsis in the studied Neonates: shows that the commonest clinical signs of studied groups were poor suckling (42 %), lethargy (30%), poor moro reflex (14%), respiratory distress (8%) and Jaundice (6%). Table 5 Comparison between groups according to laboratory parameter: The patients in Group II had the highest CRP levels (124.3 ± 71.5mg/L), lowest platelet counts (171.3 ± 45/mm3) and lowest uric acid levels (1.9 ± 0.7 mg/dl) when compared to Group I and Group III ($p<0.05$ for all comparisons).

Leukocyte, ANC, and MPV values were higher in Group I and Group II in comparison with Group III ($p<0.05$), although there was no difference between Group I and Group II for these parameters ($p>0.05$).

Table 6 Predictive values of CRP, MPV and uric acid levels

Table 7 percentage of microorganism in Group II: showing that the highest frequency was *Pseudomonas spp* and *Klebsiellaspp* in 6 cases of each spp (24% of each sp) followed by *E. coli spp* and *Candida spp.* Of 4 cases of each (16% of each spp). Regarding Streptococci spp. Was reported in 3cases (12%) and *Staphylococcispp*. Was reported in 2 cases (8%).

Table 1: Comparison Between Case (Group I & II) And Control Groups According to Demographic Data.

	Group I (Culture-proven NS) n- 50	Group II (Clinical sepsis) n- 50	Group III (Control group) n-40	P - value
Birth	12 (60%)	19 (76%)	14 (56%)	0.301
	8 (40%)	6 (24%)	11 (44%)	
Gender	10 (50%)	17 (68%)	13 (52%)	0.389
	10 (50%)	8 (32%)	12 (48%)	
Prematurity	6 (30%)	14 (56%)	11 (44%)	0.218
		11 (44%)	14 (56%)	

Table 2: Comparison Between Groups According to Birth Weight and Gestational Age.

Data	Group I (No = 50	Group II (No = 50)	Group III (No = 40)	P - value
Birth weight in (gram)	1020 -3200	1010 - 3920	1050 - 3440	0.299 NS
	2176.2 ± 663	2151.2 ± 858.6	2357.5 ± 697.3	
Gestational age in (week)	31 - 40	30 -40	30 - 40	0.617 NS

Table 3: Comparison Between Groups According to Postnatal Hospitalization Age.

Data	Group I (n=50)	Group II (n=50)	Group III (n=40)	P-value
Post-natal hospitalization age (days)	0.01*	5.0 (1-38)	2.0 (1-28)	5.5 (1-60)

P- value < 0.05 means there is significant difference between groups

Table 4: Frequency of Clinical Criteria Indicating Sepsis in the Studied Neonates

Criteria of Sepsis	Number (50)	Percentage (%)
Poor suckling	21	42 %
Lethargy	15	30 %
Poor Moro reflex	7	14 %
Respiratory distress	4	8 %
Jaundice	3	6 %

Table 5: Comparison Between Groups According to Laboratory Parameter.

Data		Group I (no = 50)	Group II (no=50)	Group III (no = 40)	P – value
Leucocytes in (mm^3)	**Range**	11.5 - 30.6	3.9 - 19.3	3.9 -12.4	< 0.001*
	Mean ± SD	17.6 ± 5.6	14.5 ± 3.9	8.4 ± 2.8	
ANC in (mm^3)	**Range**	5 - 15	1.4 - 9.8	1.3 - 7.5	< 0.001*
	Mean ± SD	9.1 ± 3.2	7.5 ± 1.7	4.5 ± 1.9	
Platelet in (mm^3)	**Range**	159 - 597	117 - 313	150 - 436	< 0.001*
	Mean ± SD	275.3 ± 107.3	171.3 ± 45	281.2 ± 72.7	
MPV in (fl)	**Range**	10.5 - 15.5	10.5 -22.1	7.7 -10.1	< 0.001*
	Mean ± SD	11.7 ± 1.3	12.2 ± 2.5	8.5 ± 0.5	
CRP in(mg/ l)	**Range**	12 - 96	12 -384	1 - 24	< 0.001*
	Mean ± SD	45.8 ± 21.9	124.3 ± 71.5	5.7 ± 6.7	
Uric acid in (mg/dl)	**Range**	1.3 - 11.6	0.9 - 3.7	2 - 6.7	< 0.001*
	Mean ± SD	3.7 ± 2.3	1.9 ± 0.7	4 ± 1.5	

* P- value < 0.05 means there is significant difference between groups

Table 6: Predictive Values of CRP, MPV and Uric Acid Levels.

	Sensitivity (%)	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
CRP	96%	95%	98%	90%	99%
MPV	100%	100%	100%	100%	100%
Uric acid	60%	90%	93%	47%	75%
CRP+ MPV	96%	100%	100%	90.9%	98%
CRP+ Uric acid	62%	95%	97%	50%	78.5%

CRP:C-Reactive Protein; MPV: Mean Platelet Volume; NPV: Negative Predictive Value; PPV: Positive Predictive Value

Table 7: Percentage of Microorganism in Group II.

Percent		**Number**	**Microorganism**
Gram -ve bacteria	*Pseudomonas spp.*	6	24%
	Klebsiella spp.	6	24%
	E- coli spp.	4	16%
	Total	16	64%
Gram + ve bacteria	*Streptococci spp.*	3	12%
	Staphylococci spp.	2	8%
	Total	5	20%
	Candida spp.	4	16%
Total		25	100

Discussion

Sepsis becomes a growing problem in NICUs due to resistant microorganisms and higher resistance to commonly used antimicrobial agents [11]. Sepsis neonatorum is the term used to describe any systemic bacterial infection documented by a positive blood culture in the first month of life. Bacterial sepsis in the neonate is a clinical syndrome characterized by systemic signs of infection accompanied by bacteremia [12].

Although a large number of studies have focused on the relationship between NS and thrombocytopenia, there are few studies investigating the association between NS and platelet kinetics [5]. It has been demonstrated that MPV values increase as a result of

raised platelet production and/or increased platelet destruction in sepsis [5].

In our study, it was revealed that MPV was higher in Group I(clinical NS) (mean =11.7±1.3) and Group II (culture proven NS) (mean=12.2±2.5) than Group III (healthy control) (mean =8.5±2.5). This is in agreement with Patrick, et al.1990 who-evaluated 156 newborns and showed that MPV was considerably higher in patients with bacteremia compared to those without NS [13] and O'Connor, et al. 1993 [14]. Study conducted by Guida et al. on patients with culture-positive sepsis and a birth weight of less than 1,500 g, pointed out that 54 % sepsis episodes were associated with thrombocytopenia and 61 % were associated with an elevation in MPV [5].

O'Connor et al. analyzed 18 neonates with coagulase-negative sepsis and demonstrated that these neonates had a higher MPV than those who did not have sepsis [14]. Their follow up was conclusive with a rapid decrease in MPV with appropriate treatment for infection. Also, Once,et al. 2012 studied a total of 100 patients with NS (35 with proven sepsis and 65 with clinical sepsis) and 50 healthy controls were enrolled. A comparison of markers of sepsis obtained at baseline revealed white blood cell count (WBC), C-reactive protein (CRP), interleukin-6 (IL-6), and MPV levels to be significantly higher in newborns with sepsis compared to healthy controls (P = 0.01, <0.001, <0.001, and 0.001, respectively) [15]. Also, Catal F,et al. evaluated the efficacy of serial Mean Platelet Volume (MPV) measurements in diagnosis and follow up of sepsis and to compare its effectiveness with C-Reactive Protein (CRP) and Interleukin-6 (IL-6) in sepsis on the day of diagnosis (1st day), 3rd, and 7th days. There were significant differences between the control and sepsis group in terms of platelet count and MPV/PDW levels ($p < 0.05$) [16]. Additionally, non-survivors with sepsis had higher levels of MPV and PDW during sepsis episodes on consecutive days ($p < 0.05$)

Our study with the above studies were not in agreement with, Cekmez, et al. who investigated the relationship between MPV and other diseases in preterm infants including NS. The authors concluded that high MPV in the first hours of life might reflect the presence of a risk factor for the development of NEC, bronchopulmonary dysplasia and intraventricular hemorrhage in extremely preterm infants [17]. However, their data indicate that higher MPV values were not associated with the development of sepsis. Also, Merza, et al. 2014 in a study on platelet Counts, MPV and PDW in culture Proven and probable neonatal Sepsis and association of Platelet Counts with mortality rate, where the study was on Four hundred and sixty-nine patients were included; 68 (14.5%) of them died. One hundred and thirty-six (29%) had culture proven sepsis, and 333 (71%) were categorized as probable sepsis. They concluded thatthrombocytopenia is a common complication of neonatal sepsis & those with thrombocytopenia have higher mortality rate & no significant difference was present between PDW and MPV of the cases who survived and died [18].

The fact that patients with sepsis had a higher MPV than those who did not have sepsis could be explained by the increase in young platelets in circulation due to platelet destruction and production if it was taken into consideration that sepsis was accompanied by thrombocytopenia. It is not very clear why the patients with proven sepsis and the patients testing positive for fungi did not differ from the patients in the other groups in terms of MPV even though they had a lower platelet count than the patients in these groups. This brings to mind the possibility that there are other factors that have a bearing on the increase in MPV as far as sepsis is concerned. In this regard, there is a need for further clinical research based on different models.

Thrombocytopenia that is well known to be associated with sepsis, in our study it was well associated with fungal sepsis. This is in agreement with Kaufman, et al. 2004 [19]. Benjamin, et al. 2000, also have demonstrated that fungal sepsis is associated with a higher degree of thrombocytopenia when compared to sepsis caused by coagulase-negative Staphylococci [20]. In another study, Scheifele, et al. 1985 reported that endotoxinemia and thrombocytopenia during neonatal necrotizing enterocolitis seemed be associated with gram negative sepsis [21].

In NS, bacteria-platelet interactions are characterized by the binding of bacteria to platelets either directly through a bacterial surface protein or indirectly by a plasma-bridging molecule that links bacterial and platelet surface receptors [22]. Ververidis, et al. discovered that thrombocytopenia to be a common finding in Necrotizing Enterocolitis (NEC) [23].

In our study, we found lower uric acid serum level with cases of neonatal sepsis and is the lowest in Group II (culture proven sepsis) when compared to Group I and III. This come in agreement with, Batra, et al. 2000 who demonstrated that uric acid levels were significantly lower in patients with sepsis [24]. Also, Similarly, Kapoor, et al.,2006 demonstrated in their research, in which they compared 44 cases of newborns with sepsis with 84 healthy newborns, that the newborns with sepsis had lower uric acid levels [25].

Also, a lot of studies in the literature talking about lowering of the serum uric acid level with neonatal sepsis. When vascular endothelial cells come in contact with bacteria, inflammatory mediators are rapidly released, this release setting into motion a rapid cascade of events. Free oxygen radicals that are generated during this cascade of events cause tissue damage by damaging DNA, denaturing proteins, and causing peroxidation of cell membrane lipids [26].

In a study by Chia et al, 2006 on Total Antioxidant Capacity (TAC) on patients with severe neonatal sepsis and uric acid level, they found that TAC correlated significantly with sepsis, and uric acid level correlated significantly with TAC [27]. Hooman, et al. 2010. Showed that higher uric acid levels served as an additive risk factor in critically ill children with sepsis [28].

As regards to MPV (using the cutoff value of 10.4fl had sensitivity, specificity, PPV, & accuracy of 100%) in our study, there was positive correlation between MPV and Leucocyte count (r=0.270, p=0.058), and CRP (r=0.267, p=0.061), while it was negative with gestational age (r=-0.006, p=0.966), birth weight (r=-0.090, p=0.535), platelet count (r=-0.177, p=0.220), and with uric acid level (r=- 0.063, p=0.633).

When we did correlation of uric acid (using the cutoff value of 3.5mg/dl, and had sensitivity 60%, specificity 90%, PPV 93%, NPV 47%, & accuracy 75%) with other parameters, we found it was positive with gestational age & birth weight, (r=0.114, p=0.431) & (r=0.006, p=0.965) respectively; while it was negative with CRP (r=-0.130, p=0.366). In our study, CRP (using the cutoff value of 9.5mg/l) had a sensitivity of 96% and specificity of 95% with a PPV of 98%, NPV of 90% and accuracy of 99%.

Compared to other researches, Adib and his colleagues reported that CRP (using the cutoff value of 12 mg/l) had a sensitivity of 45% and specificity of 95% with a PPV of 30%, NPV of 30% and correlated that with Procalcitonon (PCT). When using the cutoff value of 1.1 ng/ml, it was concluded to be a better marker than CRP in the diagnosis of neonatal sepsis due to 70% sensitivity, 80% specificity, 80% PPV and 75% NPV [29]. While research of Chan et al.,2004 showedsensitivity of 69.5% and specificity of 64.5% for PCT (using the cutoff value of 0.6 ng/ml) compared to 67.25% of sensitivity and 93.9% of specificity for CRP (using the cutoff value of 60 mg/l) [30].

Also in a similar study byAbdollahi, et al., 2012found sensitivity of 49% and specificity of 100% with a PPV of 100% and NPV of 58% for CRP (when using the cutoff value of 8 mg/l) while it has sensitivity of 76.6% and specificity of 78.2% with a PPV of 93% and NPV of 72% for PCT (using the cutoff value of 1.7 ng/ml) [31]. Also in the research of Ng, et al.,2004that was done on full term infants; sensitivity of 96% and specificity of 81% with a PPV of 71% and NPV of 97% for CD64 were obtained, compared to sensitivity of 81% and specificity of 56% with a PPV of 48% and NPV of 85% for CRP. Combination of CD64 and CRP revealed sensitivity of 100% and specificity of 80% with a PPV of 90% and NPV of 100% [32].

Conclusion

Using MPV and uric acid level as a diagnostic marker is advantageous because

- The measurement can be "quantitative" and thus enables comparison of results among different centers.
- Noninvasive utility in the diagnosis of neonatal sepsis.
- MPV can be done with CBC routinely without additional sampling.

Recommendations

We can conclude that the combined use of CRP and MPV should be considered in the early diagnosis of NS; however uric acid levels may only be utilized as an additional tool to support diagnosis.

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Abbreviations:

MPV	:	Mean Platelet Volume
NS	:	Neonatal Sepsis
CRP	:	C-Reactive Protein
CBC	:	Complete Blood Count
UA	:	Uric Acid
PPV	:	Positive Predictive Value
NPV	:	Negative Predictive Value,
NICU	:	Neonatal Intensive Care Unit
MPV/PDW	:	Mean Platelet Volume/Platelet Distribution Width
GIT	:	Gastrointestinal Tract
ITP	:	Immune Thrombocytopenic Purpura

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