Mean Platelet Volume as Predictor of Sepsis

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ABSTRACT

Introduction: Neonatal sepsis is one of the most common causes of NICU admission and one of the major causes of morbidity and mortality throughout the world. Objective of the study was to study organism-specific platelet response and to study mean platelet volume as predictor of sepsis in neonates.

Methods and Materials: Neonates admitted to single level-three intensive care units from January 2013 to 2015 were prospectively evaluated for sepsis by rapid screen test, blood counts and blood culture. In thrombocytopenic babies organism-specific platelet response and its effect on various platelet parameters were evaluated. In addition, morbidity, mortality and factors affecting survival were studied.

Results: Sepsis was diagnosed in 280 of 1100 (25%) patients. Gram-negative in 58% (161/280), Gram-positive sepsis occurred in 29% (80/280) and fungal in 4% (12/280) of patients. Thrombocytopenia was obtained in 46% (130/280) of babies. Mortality rate was higher in thrombocytopenic neonates. The frequency, severity and duration of thrombocytopenia were more with Gram-negative infection. The incidence of persistent bacteremia, multiorgan failure and death was also more in Gram-negative sepsis. Mean platelet volume was much increased in severe thrombocytopenia, Gram-negative sepsis and in non-survivors and can therefore be used as predictor of sepsis and outcome in neonates.

Conclusion: In thrombocytopenic babies with sepsis, organism-specific platelet response is seen. In addition, persistent bacteremia, multiorgan failure and death are more in these babies, and survival decreases with the increased severity and duration of thrombocytopenia. In addition MPV can be used as an early predictor of sepsis and outcome in neonates.

Keywords: Mean platelet volume, Sepsis, Thrombocytopenia

INTRODUCTION

Neonatal sepsis is one of the most common causes of NICU admission and one of the major causes of morbidity and mortality throughout the world.[1] Clinical features of sepsis are subtle, nonspecific, might be easily confused with other non-infectious causes and can rapidly lead to death if left untreated. There are early markers of sepsis like CRP, micro ESR, Procalcitonin, IL-6 and Thrombocytopenia and neonatologist has to rely on these markers for early diagnosis of sepsis. Thrombocytopenia has been used as an early but a non-specific marker for sepsis.[2] Thrombocytopenia is usually defined as a platelet count of less than 1.5lac/µl. Whereas severe thrombocytopenia is considered as platelet counts < 50thousand/µl and moderate thrombocytopenia from 50,000-1lac/µl. Thrombocytopenia can be induced by (1) increased platelet destruction (i.e. immune mechanisms, DIC) (2) decreased platelet production. Young platelets in circulation tend to be larger, since Platelet decreases in size as they become older. Increased Mean platelet volume (MPV) indicates an increased proportion of young platelets in the circulation because of increased platelet production and/ or destruction.[2] Mean platelet volume (MPV) is a machine-calculated measurement of the average size of platelets found in blood and is typically included in blood tests as part of the CBC.[3] These calculations can give the doctor additional information about platelets and/or about the cause of a high or low platelet count. A typical range of platelet volumes is 10–12 fL (femtolitre).[2] MPV is an easily accessible prognostic marker of mortality in sepsis. If one sees a sepsis patient with elevated MPV, he might attempt more aggressive therapy. MPV is easily obtained because it "is like a waste product of a complete blood count. MPV might be more specific than procalcitonin and CRP.[4]

MATERIAL AND METHODS

The G. B. Panth children hospital is the largest tertiary care children hospital of Jammu and Kashmir state, with a NICU capacity of around 110 and about 160 pediatric beds. Jammu and Kashmir is the northern state of India with an estimated population of about 7-million. This study was conducted in this hospital in year 2013 starting from January. The inclusion criteria of the study is to include all neonates who were admitted to the neonatal intensive care unit with a documented diagnosis of sepsis delivered in the same hospital; those born somewhere else but referred to the hospital because of sepsis; or neonates who developed sepsis during the period

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of hospitalization for another reason. Ethical approval was obtained from the hospital's ethics committee and informed consent was obtained from all parents. Neonates with sepsis were enrolled to the study, and those without sepsis were selected as controls. Gestational age was determined by new Ballard score and by a first trimester ultrasound scan. Maternal age, maternal medical diseases, maternal infection, and antenatal and postnatal follow-up medical problems were obtained from maternal records. Modes of delivery (vaginal or cesarean section (C/S)), gender, birth weight, and APGAR scores at 1st and 5th minutes were recorded. During the study period, infants were divided into two groups, sepsis and control (no sepsis). Sepsis was defined according to the International Sepsis Definition Conferenceas 'clinical syndrome characterized by the presence of both infection and systemic inflammatory response syndrome.' Systemic inflammatory response syndrome in the case of neonates is defined as two or more of the following: (1) tachypnea (respiratory rate >60 bpm) plus grunting/retractions or desaturation, (2) temperature instability (<36 °C or >37.9 °C), (3) capillary refill time >3 s, (4) white blood cell count (<5000 × 10^9 per l or >34000 × 10^9 per l), (4) CRP>10 mg per 100 ml or >2 s.d. above normal value, (5) interleukin 6 or 8 >70 pg ml^{-1}, (6) procalcitonin >8.1 mg per 100 ml or >2 s.d. above normal value 15,16,17,18. Sepsis is defined as one or more systemic inflammatory response syndrome criteria with signs of infection. Severe sepsis is defined as sepsis associated with hypotension or single-organ dysfunction. Septic shock is defined as severe sepsis with hypotension requiring fluid resuscitation with inotropic support. Multiorgan dysfunction syndrome is defined as the presence of multiorgan failure despite full supportive treatment. Blood was drawn from the neonates, who had the clinical signs of sepsis, from either the peripheral vein or artery for evaluation of whole blood count, Mean platelet volume (MPV), C-reactive protein (CRP) and culture at diagnosis. Blood and CSF cultures were analyzed using fully automated BACTEC method. Blood culture was done every 72 hours and complete blood count every 48 hours or whenever the clinical condition of patient would demand. Blood samples for complete blood picture were analyzed by using coulter counter machine. All cases were managed with intravenous antibiotics and other supportive measures. Initial antibiotics combination used in this hospital are: ampicillin or third generation cephalosporin and aminoglycosides, which were changed, with therapy, according to culture and sensitivity result.

This prospective study was conducted to study the value of platelet size in neonates with sepsis, and also to study whether mean platelet volume (MPV) can be used as a predictor of neonatal sepsis. Also, to determine any significant differences in platelet size (MPV) present between those due to gram- negative, gram-positive and fungal sepsis.We used SPSS software version 16 for the calculation of p- value in our study. SPSS software was used for statistical analysis in our study.

RESULTS

Out of 1100 neonates admitted in NICU, 280 babies were admitted as sepsis. As shown in the table-1.Gram negative sepsis was the commonest form of sepsis 161/280 (58%). Thrombocytopenia occurred in 130/280 (46%) babies with sepsis. Among theses babies, 27 (21%) were having mild thrombocytopenia, 29 (22%) moderate thrombocytopenia and 74 (57%) had severe thrombocytopenia. Incidence of thrombocytopenia in neonates with Gram negative sepsis was 72/161 (45%), versus gram positive sepsis 26/80 (32%). 5/12 (41%) in fungal sepsis developed thrombocytopenia. Among patients with thrombocytopenia gram negative organisms were seen in 72/130 (55%), gram positive 26/130 (16%) and fungal in 5/130 (4%) as shown in table-2. 27 neonates had clinical features of sepsis but their cultures were persistently negative. Klebsiella pneumoniae was the most common organism 48/130 (37%) followed by in Acinetobacter (12%) and E. coli (4 %) and pseudomonas in (2.3%). Among gram positive organisms staph.aureus was seen in 20/130 (15%), Enterococcus in (3%), CONS in (1.5%). Lowest Platelet countin gram negative sepsis was (48 x 10^3/µl) compared to (65 × 10^3/µl) in gram positive sepsis and (54 × 10^3/µl) in fungal sepsis (p = 0.08).The mean platelet volume initially (MPV-A), before the onset of sepsis; forgram negative sepsis was 10.1 ± 1, gram positive sepsis 10.3 ± 1.1,and fungal sepsis 10.5 ± 10.7. The difference was not statistically significant (p=0.4). MPV at the time of onset of sepsis (MPV-B) was high in gram negative sepsis than in gram positive sepsis (12.5 ± 1.2 Vs 11.4 ± 0.9) although sta-

	Gram-negative (58%)	Klebsiella	100	35.7%
		Acinetobacter	42	15%
		E. Coli	10	3.7%
		Pseudomonas	9	3.2%
	Gram-positive (29%)	Staph. Aureus	52	18.6%
		Enterococcus	11	3.9%
		CONS	17	6.1%
	Yeast (4%)	12		4.3%
	Culture-negative (9%)	27		9%
Total	N= 280			100%

Table-1: Organisms causing sepsis in neonates.

			Number	%
Organism	Gram negative 72 (55%)	Klebsiella	48	37%
		Acinetobacter	16	12%
		E. Coli	5	3.8%
		Pseudomonas	3	2.3%
	Gram positive 26 (20%)	Staph. Aureus	20	15%
		Enterococcus	4	3%
		CONS	2	1.5%
	Yeast		5	4%
	Culture negative		27	21%
Total	130			100%

Table-2: Organism distribution in thrombocytopenic neonates

Feature		Gram-negative (n=72)	Gram-positive (n=26)	Fungal (n=5)	P. value
1	Platelet nadir	48 ± 47	65 ± 42	54 ± 37	0.08
2	Mean duration of thrombocytopenia (days)	7.2 ± 5	6.3 ± 3.6	9 ± 2.9	<.02
3	Mortality	21 (29%)	6 (23%)	0	
4	(MPV-A) initially.	10.1 ± 1	10.3 ± 1.1	10.5 ± 0.7	0.4
5	(MPV-B)	12.8 ± 1.2	11.4 ± 0.9	11.7 ± 0.7	0.5
6	Multiorgan failure	20/72 (28%)	2/26 (7%)	0	<0.01

Table-3: Platelet parameters in septic, thrombocytopenic neonates.

MPV	Group	No.	MPV	P.Value
	No Sepsis	100	9.8 ± 1.01	
	Sepsis non-Thrombo-cytopenia	150	10.1 ± 1.04	<0.01
	Sepsis Throm-bocytopenia	130	12.5 ± 1.08	

Table-4: Mean Platelet Volume of thrombocytopenic and non-thrombocytopenic neonates

tistically non-significant (p= 0.5) as shown in table -3.The mean duration of thrombocytopenia in gram positive sepsis was less than fungal and gram negative sepsis. Patients with gram negative sepsis had significantly higher incidence of multiorgan failure and death. None of the patients in fungal sepsis died.For comparison of MPV, neonates admitted with neonatal jaundice without sepsis were taken as control group. Mean platelet volume of thrombocytopenic neonates was significantly higher than that of non-thrombocytopenic neonates ($p < 0.01$). The average MPV of neonates without sepsis (9.8) was lower than neonates with sepsis but with out thrombocytopenia.Highest MPV was seen in septic, thrombocytopenic neonates as shown in table-4.

While comparing survivors and non-survivors, survivors had higher weight and gestation. Non-survivors tend to have greater severity of thrombocytopenia ($p<0.01$). Mean platelet volume in case of non-survivors was also significantly higher owing to greater severity of thrombocytopenia.

DISCUSSION

The incidence of neonatal sepsis is high in developing countries (1.7–33 of 1000 live births) and in Asia, it clusters around 15 of 1000 live births.[5] A review of 11 471 blood samples from all developing nations of the world revealed that Gram-negative rods were isolated in 60% of positive cultures[5] with Klebsiella pneumoniae being the commonest organism. Similar trends were observed in our patients.Klebsiella followed by staph aureus are the most common two pathogens causing sepsis in our study. Platelets are believed to be active participants in the host defense, and the thrombocytopenia seenduring sepsis episodes may be caused, in part, by the consumption of platelets directly in these processes. They are capable of phagocytosis and can generate cytotoxic-free radicals and oxidative molecules when activated. In the present study, we have evaluated the relevance of platelet count and platelet indices(MPV), in both term and preterm babies with sepsis.Platelets not only mediate hemostasis but also have an important role in linking innate and adaptive immune systems through the expression of Toll-like receptors.[6-7] Lipopolysaccharide binds to platelets through Toll-like receptor 4, which is present on their surface, and, together with autoantibodies significantly enhances Fc-mediated platelet phagocytosis by mononuclear phagocytes.[8-9] As endotoxemia is often accompanied by a microvascular inflammatory response[10-11] cytokines and bacterial lipopolysaccharide probably trigger this response through the activation of platelets, leukocytes or both. This microvascular inflammatory response could be responsible for the multiorgan failure that occurs with sepsis.The size of platelets can predict the risk for death in patients with sepsis. Preliminary data indicate that mean platelet volume (MPV) is an easily accessible prognostic marker of mortality in sepsis.Power of WBC count and HCT may be lower than that of MPV. Successful strategies to decrease sepsis should decrease neonatal mortality rates, shorten hospital stay, and reduce costs. Therefore, we studied platele tindices to see their usefulness in early detection of neonatal sepsis. A close relationship between sepsis and thrombocytopenia has been postulated in some studies. Also, neonatal sepsis due to Gram-negative organisms had significant difference in the number of neonates with thrombocytopenia, when compared with patients with Gram-positive sepsis. Moreover, some studies have determined a specific platelet response with different degrees of thrombocytopenia to different infectious agents, including gram positive/negative and fungal infections in preterm infants.[12] Low platelet count associated sepsis were seen in both types of sepsis caused by gram negative and gram positive microorganism, and account for 46% of all of cases of neonatal sepsis in our study. Our results indicate that platelet count was observed to decrease, but MPV increased in response to sepsis. These findings suggested that sepsis affects platelet count and platelet indices. Van der Lelie et al showed that MPV was elevated in 13 of the 25 septicemia patients, and returned to normal values as soon as the disease was under control.[13] As stated earlier, one study showed that MPV falls as platelet count also decreases.[14] Therefore, previous studies are inconclusive in regards to MPV and have shown any number of MPV change during sepsis (increase, decrease, and biphasic). However, there is still some controversy regarding its reliability,whether thrombocytopenia is suggestive of one(or more) causative agents of neonatal

sepsis as other studies have identified that thrombocytopenia might not be an organism-specific marker of sepsis.[15] This may be explained by the fact that the mechanism of thrombocytopenia in septic neonates is believed to be multifactorial. Since, extensive endothelial injury,bacterial and fungal toxins, increased platelet activation,disseminated intravascular coagulation and limited responseto thrombocytopenia through platelet production and thrombopoietin in preterm infants, all are thought to be responsible factors for thrombocytopenia in infantswith sepsis.[16-17] On the other hand, it was suggested that platelet consumption rather than decrased production is the major contributor to thrombocytopenia, as it was shown that bone marrow obtained from infants with necrotizing enterocolitisthat correlated with sepsis proved normalmegakaryocyte number and maturation.[18-19] IL-6 and CRP are rapid acting acute phase proteins, and it is known that CRP increases 12 to 24 hours after the on-set of infection. It might be said that MPV is an accurate, safe and reliable marker for the diagnosis and follow up of neonatal sepsis. MPVmay be used for predicting the severity of sepsis and death with a high sensitivity and specificity at the diagnosisof sepsis and may be a useful marker for early detection of severe sepsis and predicting mortality in neonates with sepsis. Therefore, MPV is quite simple, it may be better than the other markers like procalcitonin and C-reactive protein, because they may sometimes work and sometimes they don't." MPV might be more specific, and is quite cheap because the cell sorter already produces an MPV value.

In our study, MPV was more elevated in non-survivors. Our finding is similar with that of Akarsu's research in neonates with sepsis.[20] However, our results oppose the results of Farid et al's study of patients with sepsis with no relation between MPV and Mortality.[21] The increase in mean platelet volume in septic thrombocytopenic neonates in our study had also been reported previously.[3] There is a significant differences found in relation to platelet count and MPV and to the type of microorganism causing sepsis. Previous studies reported a significant difference in relation to certain types of pathogens.[4] Similar results have been seen in our study with Klebsiella pneumoniae having maximum impact on platelet count and mean platelet volume. The platelet count and MPV was not different for different infectious agents (gram positive/ negative and fungal infections) as found by ferhat et al.[22] Additionally, they found high MPV may indicate the severity of sepsis, since non-survivors with sepsis had higher levels of MPV than survivors during sepsis episodes.[22] Similar to our results. Further work is needed for a better understanding of the basis of the observed effects of different infectious organisms on platelet counts and platelet indices, in particular; the interactions among platelets, infectious organisms, and thrombopoietin in septic neonates need to be examined. Klebsiella pneumoniae expresses a smooth lipopolysaccharide (LPS with O antigen) and a capsular polysaccharide (K antigen), and both are important for its virulence. There is a variation in the genetic makeup of O antigen between Klebsiella pneumoniae and other Gram-negative organisms, which allows Klebsiella pneumoniae strains to constitutively express a polysaccharide capsule critical for the organism's ability to resist complement-mediated opsonophagocytic killing.[23] These genetic variations in Klebsiella pneumoniae may be responsible for the persistent bacteremia and maximum effects on various platelet parameters, as seen in our study.

CONCLUSION

We concluded that low platelet count and high MPV were seen in both type of sepsis caused by gram negative microorganism and gram positive microorganism. There is statistical difference between these platelets response and the type of microorganism. Mean Platelet Volume can be used as early predictor of sepsis and outcome in neonates. Our study shows an organism-specific platelet response in thrombocytopenic babies with sepsis and the worst outcome for thrombocytopenic neonates with Gram-negative infections. We also conclude that increased MPV seen in severe thrombocytopenia is because of increased bone marrow production of immature platelets and thrombocytopenia is because of peripheral platelet destruction,not because of bone marrow suppression.

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