ORIGINAL RESEARCH PAPER

Neonatology

KEY WORDS:

DOES THE PLATELET TO NEUTROPHIL RATIO AND PLATELET TO LYMPHOCYTE RATIO PREDICT NEWBORN SEPSIS A CASE CONTROL STUDY.

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INTRODUCTION:

Death due to infections remains a major contributor to mortality in children younger than 5 years of age worldwide.(1) Sepsis is a life-threatening condition with significantly high level of mortality both in preterm and term infants.(2) Globally more than a million newborns die in Third World countries each year from infections, with a risk of neurodevelopmental impairment seen in survivors.(3-7) The incidence and etiology of early- and late-onset sepsis in neonates is variable across countries.(1,8-14). As per Indian data the incidence of neonatal sepsis according to National Neonatal Perinatal Database (NNPD) is 30 per 1000 live births (15).

The diagnosis of neonatal sepsis is difficult because many of the neonatal diseases mimic clinically as sepsis, signs and symptoms are often subtle and nonspecific, thus complicating early diagnosis and treatment. The blood culture which is considered as gold standard for diagnosing sepsis is a positive result in less than 40% of all neonatal sepsis cases. Given the low incidence of culture-positive sepsis and poor predictive value of individual complete blood cell indexes, increasing need for reliable and timely diagnostic biomarkers to efficiently diagnose sepsis.(7,16) Platelet to lymphocyte ratio is a widely used in many kinds of adult diseases such as cardiovascular diseases and malignancies (17). In this study we intend to correlate hematological parameters, platelet to neutrophil ratio and platelet to lymphocyte ratio with newborn sepsis and can these indicators be used in early identification of sepsis.

METHODOLOGY.:

This is a study done at Niloufer institute of child health neonatal intensive care unit (NICU) and is retrospective case control study conducted from August 2018 to November 2018. Study included term and nearterm new-born delivered at niloufer hospital and less than 28 days of life. Newborns were categorized in cases and control group. Cases were new-born hospitalized in the neonatal intensive care unit with symptoms suggesting neonatal sepsis including bradycardia, tachypnea, cyanosis, decrease in sucking activity, vomiting, changes in body temperature, need for oxygen therapy, need for ventilation, hypotonia, convulsion, hypotension and impaired peripheral perfusion. New-born who were healthy and no symptoms of clinical sepsis were included in the control group. Infants with perinatal asphyxia, meconium aspiration syndrome, congenital malformations, and congenital infections were excluded from the study.

All newborns included in study Peripheral blood samples were drawn during their hospital stay and CBP, CRP and blood typing were determined. CBP and other hematological parameters were calculated by the automated haematology analyser. Serum CRP concentrations were measured using nephelometry technique.

Data were analyzed and expressed as mean and standard deviations (SD) for quantitative data. Demographic and laboratory characteristics of the cases and controls sepsis were compared using t-test. All analyses were performed using Statistical package for social science (SPSS version 18.0 . SPSS Inc., Chicago, IL, USA) and statistical significance was defined as $p<0.05$.

RESULTS:

In this study total 100 new borns were included during study period, 50 in each group i.e cases and controls. Near term babies were 57 and term babies were 43 in study subjects. In total 100 subjects 53 were males (27 in cases and 26 in controls) and 47 were female babies (23 in cases and 24 in controls). Basic demographic profile of the study populations are described in table 1.

TABLE 1: basic characteristics of study population

	CASES	CONTROL
Males	27	26
Females	23	24
Term	30	27
Near term	20	23
Birth weight (mean +/- SD)	2429 +/- 327 grams	2394 +/- 593 grams
Maternal age (mean +/- SD)	22.8 +/- 2.9 years	23.6 +/- 3.7 years
Mode of delivery (NVD/LSCS)	29/21	32/18
Gestational age (mean +/- SD)	36.1 +/- 3.1 weeks	35.9 +/- 2.7 weeks

As for the hematological variables compared in cases and control group hemoglobin, hematocrit, lymphocytes, platelet distribution width, and platelet to neutrophil ratio were not statistically significant between two groups (p value > 0.05). Wbc counts, netrophils, platelet counts, platelet to lymphocyte ratio and red cell distribution width were statistically significant between cases and control groups (p value < 0.001). Platelet to neutrophil ratio in sepsis cases group was 47.0 +/- 33.9 and in control was 58.9 +/- 43.1 which was not statistically significant p value of more than 0.05. Platelet to lymphocyte ratio in sepsis cases group was 62.28 +/- 36.24 and in control was 82.28 +/- 49.8 which was statistically significant p value of less than 0.05.

TABLE 2: hematological variables between cases and control groups

Variable	Cases	Control	T value	P value
Hemoglobin	15.1 +/- 4.1	15.65 +/- 3.46	-0.68	0.24
Hematocrit	46.2 +/- 11.6	47.94 +/- 11.4	-0.80	0.21
Wbc count	9259.6 +/- 4351.2	12933.5 +/- 5158.6	-3.86	0.0001

Neutrophils	4601.8 +/- 3293.9	7460.8 +/- 5051.4	-3.35	0.0005
Lymphocytes	3150.6 +/- 1704.4	4512.4 +/- 1572.9	-1.24	0.10
Platelet count	159466.6 +/- 91394.6	246850.4 +/- 133900.2	-3.86	0.0001
Platelet disribution width	12.88 +/- 3.03	12.23 +/- 2.39	1.17	0.12
RDW	18.6 +/- 1.48	15.96 +/- 1.27	11.11	0.0001
Platelet to Neutrophil ratio	47.0 +/- 33.9	58.9 +/- 43.1	-1.33	0.09
Platelet to Lymphocyte ratio	62.28 +/- 36.24	82.8 +/- 49.8	-2.24	0.013

DISCUSSION:

During neonatal sepsis, leucocytes and platelets are more frequently affected than red blood cells. The most frequently encountered features are an abnormal total leukocyte count, an abnormal total neutrophil polymorphonuclear neutrophil (PMN) count, an elevated immature PMN count, an elevated immature to total PMN ratio, an abnormal immature to mature PMN ratio, a low platelet counts. During neonatal bacterial infections, increased proinflammatory cytokines cause an initial and transient neutrophilia but also neutropenia. According to recent, larger datasets, both a high count and a low count of lymphocytes at birth can be significantly associated with early onset sepsis. Neonatal thrombocytopenia is commonly considered as an additional marker of the severity of sepsis and has been identified as a potent predictor of sepsis associated mortality. (18) Typical diagnostic parameters as mentioned above white blood count (WBC), absolute neutrophil count (ANC), immature/total neutrophil (I/T) ratio, and variably obtained C-reactive protein (CRP) have low sensitivity and are nonspecific, often demonstrating increased level response to various other neonatal diseases.(19-23) Thus, early, accurate, and rapid diagnosis of neonatal sepsis remains a major diagnostic challenge in neonatol ogy, revealing the need for reliable and timely diagnostic biomarkers in neonatal sepsis.

One such reliable marker in recent studies is platelet to lymphocyte ratio (PLR). PLR is a widely available, effective, and simple marker. Many previous studies reported a significant association between increased PLR and major adverse outcomes in cardiovascular diseases, and reduced survival in adult malignancies.(24-28) In study done by Toprak et al concluded that important relation between PLR values of more than 117.14 and the occurrence of PPROM. Moreover, it was found to be a significant independent discriminator for PPROM, a condition that leads to adverse maternal and neonatal events. PLR is a cost effective, easy to use, and practical marker that can be used for the early diagnosis of PPROM, which can help to provide maternal and fetal well-being.(17)

In this study platelet to lymphocyte ratio statistically significant between sepsis and control group with p value of less than 0.05. In this study we could not find any correlation between platelet to neutrophil ratio in sepsis and control group although further studies with large sample size could establish any further correlation. In recent studies done established correlation between Red cell distribution with sepsis and this study also Red cell distribution width was statistically significant between sepsis and control group. (29)

We conclude that rapid, in-expensive, and readily available indicators like platelet to lymphocyte ratio and red cell distribution width can be used as markers for early identification of sepsis and help clinician in early initiation of appropriate management. Although further larger studies are needed to establish these markers as early indicators for sepsis.

REFERENCES:

1. Vineet Bhandari. Effective Biomarkers for Diagnosis of Neonatal Sepsis. Journal of the Pediatric Infectious Diseases Society pp. 1–12, 2014. DOI:10.1093/jpids/piu063.
2. Senem Alkan Ozdemir, Esra Arun Ozer, Ozkan Ilhan, Sumer Sutcuoglu. Can neutrophil to lymphocyte ratio predict late-onset sepsis in preterm infants?. J Clin Lab Anal. 2017;e22338,1 of 5. https://doi.org/10.1002/jcla.
3. Garcia-Prats JA, Cooper TR, Schneider VF, Stager CE, Hansen TN. Rapid detection of microorganisms in blood cultures of newborn infants utilizing an automated blood culture system. Pediatrics. 2000;105(3 Pt 1):523–527.
4. Stoll BJ, Hansen NI, Adams-Chapman I, et al. National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA. 2004;292(19): 2357–2365.
5. Ganatra HA, Stoll BJ, Zaidi AK. International perspective on early-onset neonatal sepsis. Clin Perinatol. 2010;37(2):501–523.
6. Pappas A, Kendrick DE, Shankaran S, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Chorioamnionitis and early childhood outcomes among extremely low-gestational-age neonates. JAMA Pediatr. 2014;168(2):137–147.
7. Pradeep Mally, Jie Xu, Karen D Hendricks-Muńoz. Biomarkers for neonatal sepsis: recent developments. Research and Reports in Neonatology 2014:4 157–168. http://dx.doi.org/10.2147/RRN.S48316.
8. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012; 379: 2151–61.
9. Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. Arch Dis Child Fetal Neonatal Ed 2011; 96:F9–14.
10. Tosson AM, Speer CP. Microbial pathogens causative of neonatal sepsis in Arabic countries. J Matern Fetal Neonatal Med 2011; 24:990–4.
11. Kohli-Kochhar R, Omuse G, Revathi G. A ten-year review of neonatal bloodstream infections in a tertiary private hospital in Kenya. J Infect Dev Ctries 2011; 5:799–803.
12. Sgro M, Shah PS, Campbell D, et al. Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008. J Perinatol 2011; 31:794–8.
13. Morioka I, Morikawa S, Miwa A, et al. Culture-proven neonatal sepsis in Japanese neonatal care units in 2006–2008. Neonatology 2012; 102:75–80.
14. Hornik CP, Fort P, Clark RH, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev 2012; 88 Suppl 2:S69–74.
15. Singh M. Care of the Newborn, 8th ed. New Delhi: CBS Publishers & Distributors:2015:219-85
16. Clarissa Deleon,Karen Shattuck, Sunil K. Jain. Biomarkers of Neonatal Sepsis. NeoReviews Vol.16 No.5 May 2015 e297.
17. Erzat Toprak, Murat Bozkurt, Burcu Dinçgez Çakmak, Emel Ebru Özçimen, Musa Silahl, Ayşe Ender Yumru, Eray Çalışkan. Platelet-to-lymphocyte ratio: A new inflammatory marker for the diagnosis of preterm premature rupture of membranes. J Turk Ger Gynecol Assoc 2017; 18: 122-6
18. Paolo Manzoni.Hematologic Aspects of Early and Late-Onset Sepsis in Preterm Infants. Clin Perinatol 42 (2015) 587–595. http://dx.doi.org/10.1016/j.clp.2015.04.012.
19. Christensen RD, Baer VL, Gordon PV, et al. Reference ranges for lymphocyte counts of neonates: associations between abnormal counts and outcomes. Pediatrics. 2012;129(5):e1165–e1172.
20. Chiesa C, Natale F, Pascone R, et al. C reactive protein and procalcitonin: reference intervals for preterm and term newborns during the early neonatal period. Clin Chim Acta. 2011;412(11–12):1053–1059.
21. Ng PC, Lam HS. Biomarkers for late-onset neonatal sepsis: cytokines and beyond. Clin Perinatol. 2010;37(3):599–610.
22. Lam HS, Ng PC. Biochemical markers of neonatal sepsis. Pathology. 2008;40(2):141–148.
23. van Dissel JT, van Langevelde P, Westendorp RG, Kwappenberg K, Frölich M. Anti-inflammatory cytokine profile and mortality in febrile patients. Lancet. 1998;351(9107):950–953.
24. Nikolsky E, Grines CL, Cox DA, Garcia E, Tcheng JE, Sadeghi M, et al. Impact of baseline platelet count in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction (from the CADILLAC trial). Am J Cardiol 2007; 99: 1055-61.
25. Nording HM, Seizer P, Langer HF. Platelets in inflammation and atherogenesis. Front Immunol 2015; 6: 98.
26. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets 2015; 26: 680-1.
27. Sahbaz A, Cicekler H, Aynioglu O, Isik H, Ozmen U. Comparison of the predictive value of plateletcrit with various other blood parameters in gestational diabetes development. J Obstet Gynaecol 2016; 36: 589-93.
28. Ekin A, Gezer C, Kulhan G, Avcı ME, Taner CE. Can platelet count and mean platelet volume during the first trimester of pregnancy predict preterm premature rupture of membranes? J Obstet Gynaecol Res 2015; 41: 23-8.
29. Cosar H, Yilmaz O, Temur M, Ozun Ozbay P, Bulut Y and Karakulak M. Relationship between Early-Onset Neonatal Sepsis and Red Blood Cell Distribution Width (RDW). J Hematol Thrombo Dis, an open access journal, Volume 5, Issue 2, 266.