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COMPARISON OF THE PERCENTAGE OF NRBC/100 WBC IN EARLY ONSET SEPSIS AND NON-INFECTIOUS PREMATURE INFANTS

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Abstract. *Introduction.* In spite of significant advances in medical care, neonatal sepsis remains an important risk factor for neonatal morbidity and mortality. Accordingly, the present study was conducted to compare the number of nucleated red blood cells per 100 white blood cells (NRBC/100WBC) in neonates with early onset sepsis and non-infectious neonates. *Materials and methods.* In this cross-sectional study of 154 neonates admitted to the NICU of Ghaem Hospital in Mashhad, Iran within the first three days of life, during 2014 to 2018, the characteristics of 44 neonates identified early onset sepsis (Case group) were compared with 110 non-infectious neonates (Control group). After the confirmation of sepsis in neonates based on positive blood culture and laboratory results, a researcher-made questionnaire containing neonatal characteristics (gestational age, weight, first minute Apgar scores, fifth minute Apgar score, duration of oxygen therapy, and mechanical ventilation duration) and neonatal laboratory profiles (routine blood culture, WBC, NRBC/100WBC, CRP, blood glucose, calcium and venous blood gas) was filled in. *Results.* The results of this study showed that the absolute number of NRBC/mm^3 in control group was 56.07±86.65 and in case group was 592.70±1166.75 ($p = 0.000$). Also, the number of NRBC per 100 white blood cells in control group was 6.54±11.18 and in case group was 31.84±40.07 ($p = 0.000$). The absolute number of NRBC/mm^3 for the detection of early onset sepsis had a good sensitivity (78%) and NRBC/100WBC was suitable specificity (68.2%). *Conclusion.* This study indicated that NRBC/100 WBC and absolute NRBC count/mm^3 can be helpful in the diagnosis of early onset sepsis and have an acceptable sensitivity and specificity.

Key words: *early onset sepsis, nucleated red blood cells (NRBC), neonates, blood culture, infection, prematurity.*

СРАВНЕНИЕ ВЕЛИЧИН ОТНОШЕНИЯ «ЯДРОСОДЕРЖАЩИЕ ЭРИТРОЦИТЫ/100 ЛЕЙКОЦИТОВ» (NRBC/100 WBC) У НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ С РАННИМ РАЗВИТИЕМ СЕПСИСА И БЕЗ ИНФЕКЦИОННОЙ ПАТОЛОГИИ

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Резюме. *Введение.* Несмотря на значительный прогресс в области оказания медицинской помощи, неонатальный сепсис остается важным фактором риска неонатальной заболеваемости и смертности. Настоящее исследование было проведено для сравнения величин отношения ядросодержащих эритроцитов к 100 лейкоцитам (NRBC/100WBC) у недоношенных новорожденных с ранним началом сепсиса и без инфекционной патологии. *Материалы и методы.* В поперечное исследование было включено 154 новорожденных, поступив-

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ших в отделение интенсивной терапии больницы Гаем в Мешхеде, Иран, в течение первых трех дней жизни в период с 2014 по 2018 г. У 44 новорожденных обнаружены признаки раннего сепсиса (группа сепсиса), 110 новорожденными не имели инфекционной патологии (контрольная группа). После подтверждения сепсиса на основании положительных результатов посева крови и лабораторных исследований, проанализировали составленный нами вопросник, содержащий характеристики новорожденных (гестационный возраст, вес, оценка по шкале Апгар на первой минуте, оценка по шкале Апгар на пятой минуте, продолжительность кислородной терапии и продолжительность искусственной вентиляции легких) и неонатальные лабораторные профили (образцы пуповинной крови, общий анализ крови, абсолютное количество ядросодержащих эритроцитов в мм^3 (NRBC/мм^3), отношение количества ядросодержащих эритроцитов к 100 лейкоцитам (NRBC/100WBC), С-реактивный белок). *Результаты* исследования показали, что абсолютное количество NRBC в контрольной группе составляло 56,07±86,65/мм^3, а в группе сепсиса — 592,70±1166,75/мм^3 (p = 0,000). Кроме того, количество NRBC на 100 лейкоцитов в контрольной группе составляло 6,54±11,18, а в группе сепсиса — 31,84±40,07 (p = 0,000). Метод определения абсолютного количества NRBC/мм^3 показал хорошую чувствительность (78%), а подсчет соотношения NRBC/100WBC — неплохую специфичность (68,2%) для выявления раннего начала сепсиса. *Заключение.* Отношение NRBC/100WBC и абсолютное количество NRBC/мм^3 могут быть полезны в диагностике сепсиса у недоношенных новорожденных и демонстрируют приемлемую чувствительность и специфичность.

Ключевые слова: *ранний сепсис, ядросодержащие эритроциты (NRBC), новорожденные, гемокультура, инфекция, недоношенность.*

Introduction

Neonatal sepsis is a major cause of neonatal mortality. Therefore, rapid and timely identification of infected neonates is crucial in proper management of these patients [6]. Sepsis and infection are reported as the first (80%) and fourth (25.3%) most common cause of neonatal deaths. Early identification of neonatal sepsis increases the chance of neonates' recovery and reduces their complications [6]. In general, the diagnosis of infections in neonates is challenging due to non-specific symptoms as well as the absence of a definitive diagnostic test [4]. Neonatal clinical symptoms such as poor feeding, lethargy, bradycardia, hypothermia, hypotension, seizure, respiratory distress, etc. are non-specific for diagnosis of neonatal sepsis. Body fluids culture (blood and cerebrospinal fluid) is the gold standard for the diagnosis of neonatal infections, however, it takes 48–72 hours for the results to be available. Laboratory findings including complete blood cell count and laboratory and immunological tests have lower sensitivity and specificity than blood culture [4, 5, 6]. Nucleated red blood cells are, in fact, premature erythrocytes in the peripheral blood, leading to an increase in the peripheral blood in response to increased erythropoietin. Erythropoietin is a glycoprotein hormone secreted by the kidneys, liver, spleen, lungs, and bone marrow in response to hypoxemia [8]. Many acute and chronic stimuli increase the number of NRBC in blood circulation by increasing the activity of erythropoietin [14]. Dulay et al. (2008) examined the number of NRBC in neonates with early onset sepsis delivered at earlier gestational ages (mean±SD: 27.1±2.8 weeks) and found that it increased, and 83.9% of cases of early onset sepsis were confirmed and 48.9% of suspicious cases significantly increased [10].

Increasing the number of NRBCs in embryonic circulation may be secondary to hypoxia or inflammation [20]. Previous studies have shown that the inflammatory response associated with the release of cytokines, especially IL-6, can be led to an increase in the production of NRBC [23]. Both fetus inflammatory response and stress may play a role in the production or release of NRBC in the peripheral circulation. In addition, in pregnancies with histologic chorioamnionitis, host inflammatory response may be independent of erythropoietin resulting in increased fetal NRBC [21]. In one study, NRBC count in the peripheral blood smear helps with the diagnosis of neonatal infection and can be used in conjunction with other laboratory tests as a simple and convenient method [7].

As the number of nucleated red blood cells is one of the simple, available, and fast response factors, it can play an important role in facilitating the diagnosis of sepsis if it helps in early detection of the infection. Therefore, a case-control study was designed to evaluate the number of nucleated red blood cells in preterm neonates with early onset sepsis and compare them with non-infected neonates.

Materials and methods

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. This cross-sectional study (from 2013 to 2019) was performed on 154 neonates hospitalized in the first three days after birth, in Ghaem Hospital, Mashhad, Iran, using convenient sampling method. Ghaem Hospital is a general referral hospital with NICU (12 beds), level 2 care (25 beds) and a maternity hospital (Level 1 care), which has about 3000 births annually. The written informed consent was obtained from the parents of the neonates. Neonates

with Apgar scores less than 7 at 5 minutes after birth, congenital malformations, congenital TORCH infections, hemolytic anemia, and erythroblastosis fetalis were excluded from the study.

All the neonates entered the NICU in the first day of life were examined. Clinical and laboratory evaluation of patients was performed based on clinical examination guidelines. Data was extracted from neonatal medical history including gestational age, weight, 1 min Apgar score, fifth-minute Apgar score, duration of oxygen therapy and duration of mechanical ventilation) and neonatal laboratory characteristics (such as routine blood culture (Trypticase soy broth), WBC, NRBC/100WBC, CRP, blood glucose, calcium and Venous blood gas). The blood sample with EDTA, collected for the routine tests, was used for complete cell count, followed by peripheral blood smear analysis (by Giemsa staining). The cells were separated and the number of nucleated red blood cells (NRBCs) per 100 white blood cells was reported. Neonates who had a positive blood culture were considered as the case group. Early onset sepsis was considered based on its onset at 0 to 3 days of age. The neonates who had a negative blood culture and had no clinical and laboratory evidence of infection were considered as control group. The NRBC/100WBC and the number of absolute NRBC were compared between these two groups. SPSS version 23 was used to analyze the data. Statistical comparisons were performed by Mann–Whitney test, unpaired t-test and Chi-square test as required. Receiver-operating characteristic (ROC) curves were also constructed allowing the calculation of positive and negative predictive values. Analysis of covariance was used to control the variable of gestational age. A p-value ≤ 0.05 was considered as the cutoff for significant difference between groups.

Results

A total of 286 infants were enrolled in the study; 31 were diagnosed with significant asphyxia, 26 with intrauterine growth retardation, 11 with congenital anomaly or infection, 6 with hemolytic anemia, 6 with maternal preeclampsia and 18 had maternal diabetes. Finally 22 neonates died in the 1st week and 12 with incomplete follow-up and were excluded from the study. The reported germs included: 12 cases of *Klebsiella pneumoniae* (27.27%), 10 cases of *Enterobacter* (22.72%), 10 cases of *Staphylococcus epidermidis* (22.7%), 6 cases of *E. coli* (13.63%), 4 cases of *Acinetobacter* (9.09%), and 2 cases of coagulase-negative *Staphylococci* (4.54%). Laboratory findings are summarized in Table.

The results of this study demonstrated that there was statistically significant difference in terms of the gestational age ($p = 0.001$) between the two groups (neonates who had a negative blood culture and those who had a positive blood culture). However, after adjusting for gestational age using the analysis of covariance, there was a statistically significant difference between the two groups in NRBC levels ($p = 0.000$). There was a significant difference between two groups in CRP ($p = 0.090$), WBC ($p = 0.006$), NRBC/mm^3 ($p = 0.000$), and NRBC/100 WBC ($p = 0.000$). In other word, these variables in the neonatal group who had a positive blood culture were significantly higher than those of non-infected neonates (Table).

The results of this study showed that the number of NRBC/100 WBC and absolute number of NRBC/mm^3 increased in neonates with early onset sepsis. In the diagnosis of neonatal sepsis, the number of NRBC/100 WBC greater than 5 had a sensitivity of 72% and the specificity of 58%, and the absolute NRBC count greater than 400/mm^3 had sensitivity of 84.6% and specificity of 64% (Figure).

Discussion

Early onset sepsis microorganisms are commonly encountered in the genitourinary tract of mother and cause the infection of the amniotic fluid, placenta, cervical or vaginal canal. In the event of a rupture of the membrane or before labor begins, the infection occurs in the amniotic fluid [4, 22]. The main causes of neonatal sepsis in advanced countries are *Streptococcus* group B, *E. coli* and *Listeria monocytogenes*, and in developing countries are gram-negative bacilli, coagulase negative *Staphylococci* and other bacteria [16]. In the present study, the most common causes of early onset sepsis were *Klebsiella* (25%), *Enterobacter* (22.7%), *Staphylococcus epidermidis* (22.7%) and *E. coli* (11.35%). In a study conducted by Farhat et al. (2014), the most common bacteria in neonatal sepsis in blood culture were coagulase negative *Staphylococcus* (35%), followed by *Staphylococcus aureus* (24%) and *Klebsiella* (18%) [11]. In a previous sudy, the most common bacteria in neonatal sepsis were gram-negative bacteria (55%) and coagulase negative *Staphylococcus* (34%) and other gram-positive bacteria (10%) [3]. In a similar another study in this center, 44% of the isolated microorganisms were coagulase negative *Staphylococcus*, followed by *Klebsiella pneumoniae* (31%), *E. coli* (19%), and other gram-negative microorganism (6%) [18]. The difference in the prevalence rate of microorganisms might be due to difference in sampling as well as that we studied only the early onset sepsis.

In this study, the number of WBCs in the neonatal group who had a positive blood culture was higher than that of non-infected neonates. The results of Hornik et al. (2012) showed that the number of WBC had a low correlation with early onset sepsis. The specificity of the WBC less than 5000 per mm^3 and the WBC count below 1000 per mm^3 to detect sepsis was high, but with low sensitivity [15].

Table. Comparison of the mean neonatal variables between case and control groups

Groups / Variables	Control group 110 [71.4%]	Case group 44 [28.6%]	p value
CRP (Mg/dl)	8.94±16.11	23.90±28.49	0.090
WBC	9.64±5.79	14.82±11.64	0.006
NRBC absolute count (mm^3)	56.07±86.65	592.70±1166.75	0.000
NRBC/100 WBC	6.54±11.18	31.84±40.07	0.000
Neutrophil percentage	45.07±41.61	44.32±21.36	0.867
Lymphocyte percentage	47.51±18.27	44.18±21.13	0.113
Platelet (per mcL)	250.48±157.73	172.70±106.60	0.845
1 min Apgar score	7.03±1.72	5.93±1.81	0.541
Fifth minute Apgar score	8.00±1.32	7.53±1.06	0.566
Weight (g)	1641.04±660.03	1350.22±606.23	0.382
Duration of oxygen therapy (day)	3.35±7.14	6.68±7.99	0.052
PT	15.16±3.01	19.39±4.67	0.319
PTT	74.50±29.99	63.00±28.88	0.643
Urea (mg/dl)	48.24±32.93	67.85±28.89	0.071
BUN (mg/dl)	60.09±20.20	39.00±13.06	0.077
Cr (mg/dl)	1.05±1.52	0.70±0.23	0.340
Sodium (mg/dl)	139.76±4.15	134.32±18.85	0.052
Calcium (mg/dl)	9.07±0.99	8.55±11.36	0.073
Blood glucose(mg/dl)	78.00±11.58	92.00±14.98	0.074
Ph1	7.29±0.14	7.28±0.12	0.858
be	7.71±0.79	7.17±0.92	0.974
Hco3a	21.31±4.32	22.74±4.48	0.316
Pco2a	43.08±18.62	48.46±10.91	0.324
HCT	41.45±7.55	43.57±7.08	0.135
Gestational age (wk)	30.23±3.10	32.85±3.90	0.001

Note. The values are based on standard deviation±mean.

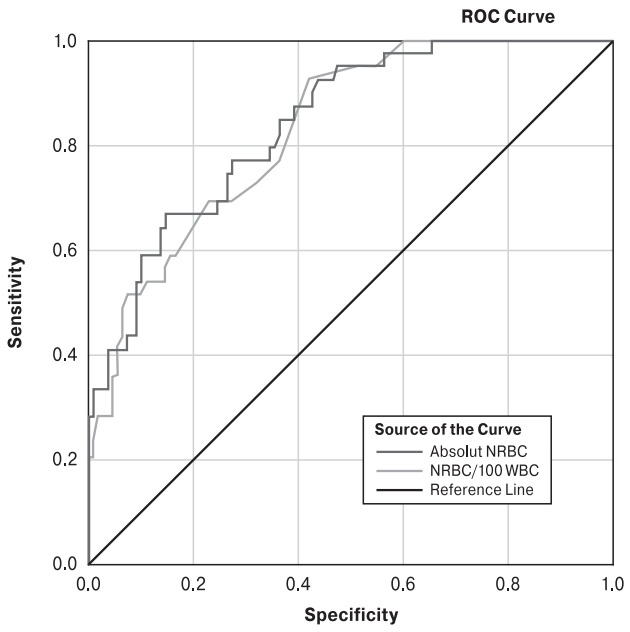

Figure. Comparison of the sensitivity and specificity of NRBC numbers in 100WBC and NRBC absolute count in the diagnosis of neonatal sepsis

The results of the current study showed that in the confirmed early onset sepsis, the number of NRBC/100 WBC was about 5 times greater than non-infected neonates, and the absolute number of NRBC/mm^3 was nearly ten times greater than non-infected neonates. During the first 12 hours, the number of NRBCs decreased by 50% and reached 20 to 30 in mm^3 in the first 48 hours. In a healthy term neonate after 3 to 4 days, NRBC was not normally seen in the peripheral blood. However, preterm neonates may have NRBC in the peripheral blood up to one week after birth [2, 9, 12]. A similar showed that inflammatory response is associate with release of cytokines and the increase of NRBC [23]. Ranganathan reported the increase NRBC in the blood to be associated with an increased risk of early onset sepsis [19]. In a study by Dulay et al., who studied 68 preterm neonates, NRBCs and other inflammatory factors in the diagnosis of early onset sepsis were compared and a direct relationship between NRBC and IL-6 was reported in the diagnosis of neonatal sepsis [10]. Leikin et al. performed a study on 359 neonates of the mothers with chorioamnionitis, and found that there was a significant correlation between NRBC and pathological chorioamnionitis [17].

In the diagnosis of neonatal sepsis, NRBC/100 WBC more than 5 had the sensitivity of 72% and specificity of 58%, and the absolute number of NRBC greater than 400 had a sensitivity of 84.6% and specificity of 64%. In a study conducted by Abhishek and Sanjay, number of NRBCs was increased in all 14 neonates and had a sensitivity of 35% and a specificity of 53.48% to detect sepsis [1]. In a similar study, sensitivity and specificity of NRBC count more than 10 were reported as 45% and 83% to detect infection [7]. Therefore, this simple, fast, and cost-effective test can be used to identify early onset sepsis and reduce the mortality and morbidity of the neonates.

One of the limitations of our study was the selection of the group of premature infants without infection. Premature infants often have different morbidities and it is difficult to find healthy premature neonates. Also, convenient sample size and thereby overlapping confidence intervals were other limitations of our study.

Conclusion

In neonates with confirmed early onset sepsis, NRBC/100 WBC and the absolute number of NRBCs increased by about 5–10 times greater than non-infectious neonates. The NRBC number per 100 WBC greater than 5 had a suitable sensitivity and the absolute number of NRBC greater than 400 had high sensitivity to the diagnosis of early onset sepsis.

"What This Study Adds"

The NRBC number per 100 WBC greater than 4 has a suitable sensitivity and the absolute number of NRBC greater than 400 had high sensitivity for the diagnosis of early onset sepsis.

"What is Already Known"

Neonatal sepsis is a the major cause of neonatal mortality and rapid and timely identification of infected neonates plays an important role in the treatment of these patients.

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