Evaluation of neonatal sepsis and assessment of its severity by Red Cell Distribution Width indicator

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Abstract

Background: Neonatal sepsis remains a challenge for neonatal care providers. **Aim:** to measure red cell distribution width percent (RDW %) as a marker for neonatal sepsis severity and to correlate the determined severity with other indicators. **Methods:** This case control study was carried out at neonatal intensive care unit at Assiut Al Azhar University Hospital from June to December 2015. Ethical Research Committee Approval and written consents were obtained from parents of the neonates 50 neonatal sepsis cases and 30 normal controls. Inclusion criteria: age from 1-28 days and had findings of sepsis either clinical or laboratory. Neonates were subjected to: History taking, clinical examination for manifestations of sepsis. Complete blood count- C- reactive protein, Blood culture and sensitivity and determination of RDW % were done to all neonates. **Results:** Mean RDW % was higher among cases than controls (18.35± 1.79 & 12.95± 2.23 respectively) ($P < 0.001$), meanwhile hemoglobin (HB) was lower in cases than controls $P=0.094$. WBCs were higher among cases compared to control ($P =0.030$). CRP was normal in all controls, and was higher in all cases. RDW % was higher in severe sepsis than mild (19.4 ± 1.8 % & 17.2± 0.58% respectively) ($P < 0.0001$), while HB and WBCs showed insignificant relation with severity of sepsis ($p =0.299$ and 0.129 respectively). CRP showed significant relationship with severity of sepsis $p<0.01$**. Conclusion:** RDW % can serve as a marker and prognostic indicator in assessing severity evaluation and risk stratification of neonatal sepsis.

Keywords: Neonatal, Sepsis, RDW. Evaluation, indicator

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Introduction

Neonatal sepsis is characterized by presence of bacteraemia and clinical manifestations caused by microorganisms and their toxic products [(1).] Criteria for diagnosis of neonatal sepsis should include infection documentation with a systemic illness in which non-infectious explanations for the abnormal Patho-physiologic state are excluded or unlikely [(2)].

Incidence of such problem has declined over the past decades and despite of this decline, it is still considered the leading etiology of morbidity and mortality in the neonates [(3).] 88% of all neonatal deaths in the community are attributable to infectious factors with considerable

fluctuations overtime and geographic locations [4]. In the United States, neonatal sepsis affects up to 32,000 live births annually, with an incidence of 1 to10 cases per 1000 live full-term births and 1 per 250 live premature births [5].

When neonatal sepsis identified early and accurately degree of severity can be easily determined which help proper management. Therefore, recognizing a single marker or set of markers for diagnosis of such problem may help decrease the global impact of sepsis [6]. 180 markers had been evaluated for neonatal sepsis, but none of these markers was sensitive or specific enough to be adopted as standard of care. Numbers of publications have highlighted the potential use of RDW% in diagnosis and / or prognosis of sepsis in neonates [7]. Prognostic markers in sepsis are of great interest. The ability to provide diagnosis based on a routinely marker which can be easily available on a CBC would be greatly helpful in assessing the severity of illness. Recently several studies showed that high RDW value can predicts diseases severity especially morbidity and mortality in patients admitted to ICU [8].

RDW considered a measure of the variation of RBC volume that is reported as part of a standard CBC. Usually RBCs are of standard size (about 6-8 μm in diameter) however, certain disorders can cause a significant variation in cell size, thenormal reference rangeof RDW in human RBCs is 11.5-15.5%. Mathematically RDW is calculated with the following formula: RDW = (Standard deviation of MCV ÷ mean MCV) × 100. RDW is a way to measure RBCs volume and size. When RBCs are larger than normal, this may indicate a problem [9]. In recent study, RDW has a potential prognostic power in critically ill patients. RDW is a very useful and strong independent predictor of mortality and morbidity in ICU patients [10].

Aim of the study

To identify if RDW % can be used as a marker for diagnosis neonatal sepsis severity, and to correlate severity of sepsis determined by RDW% with other known indicators.

Subjects and Methods

This study was conducted at neonatal intensive care unit (NICU) at Al-Azhar Assiut University teaching Hospital from June 2015 to December 2015. Protocol of the study was approved by the faculty Institutional Scientific and Ethical Committee, and written consents were obtained from the parents of neonates. Study sample was divided into two groups: Group I (cases) comprised of 50 patients (20 males and 30 females) aged from 1-28 days, who had clinical or laboratory findings of sepsis such as fever, breathing problems, diarrhea, reduced suckling. Inclusion criteria of cases were full term, preterm, normal birth weight, low birth weight and very low birth weight, cases then subdivided into 2 groups, mild sepsis (n= 24) , and severe sepsis (n=26). Classification of cases into sever and mild was based on both clinical and laboratory findings, clinical findings as degree of fever, ability of suckling and breathing, presence or absence of diarrhea while laboratory findings as CRP, WBCS, HB and PLT [8]. Neonates suffering from Congenital anomalies, perinatal asphyxia and those with birth trauma were excluded from the study

While group II (control) includes 30 apparently healthy (16 males and 14 females) neonates, matched by age and

sex with the patients. All neonates were subjected to the following: Full history taking including prenatal, natal, postnatal history of symptoms and signs of sepsis and invasive procedures that were done to the baby after delivery. Full Clinical examination for early and late symptoms and signs of sepsis as: temperature, apnea, instability, need for oxygen therapy, need for ventilation, bradycardia or tachycardia, hypotension with hypo-perfusion, feeding intolerance and abdominal distension. For both patients and control groups, the following investigations were done: CBC, C – reactive protein (CRP), Blood culture and sensitivity.

CBC including total leucocytic count, hemoglobin level, platelets count and estimation of red cell distribution width coefficient variation (RDW-CV) was performed on the ABBOTT CELL-DYN 3700 automated hematology analyzer. A laser beam is focused on the flow cell .As the sample stream intersects the laser beam, the light scattered by the cells is measured at four different angular intervals [(11).] Estimation of CRP level in the serum was done using latex agglutination test)(OMEGAKIT) with cut off 6 mg/L. furthermore blood Cultures were performed using neonatal blood culture bottles (Egyptian Diagnostic Media) for all patients then incubated for up to 7 days at 37°C, under aerobic condition. Subculture was done on 3rd, 5th and 7th day on blood agar, chocolate agar, mannitol salt agar and Mac Conkey's agar plates. Colonies grown on these different media were then subjected to further biochemical and morphological identification according to the standard microbiological methods [(12).] The most important organisms grown was group beta streptococci, E.coli and Listeria monocytogenes.

Statistical analysis of data:

Statistical package for social science (SPSS) version 16 was used for data processing. Data were analyzed and expressed as mean and standard deviations (SD) for quantitative data. Chi square test was used to compare qualitative parametric variables while fisher exact test was used in non parametric qualitative variables; independent sample t test to compare means of parametric quantitative variables. Values were considered significant when P values were equal to or less than 0.05.

Results

Table (1) shows that although females were higher among cases than controls, the difference was not statistically significant, it also shows that more than half of cases were preterm (54%), full term were 46% and 43.3% for cases and controls respectively. This difference was not statistically significant. Nearly half of the cases had mild disease (48%) and (52%) had severe disease. Early onset neonatal sepsis was seen in nearly three quarters of the cases (74%) while 26% of them had late onset of sepsis.

Table (2) shows that although HB level was lower in cases compared to the controls (14.5 compared to 15.4), the difference was not statistically significant. On the other hand, WBCs were significantly higher among cases compared to controls (16.5 vs 13.2 respectively). Moreover, platelet count showed a statistically significant difference between cases and control (232.7 vs 377.7 respectively). CRP was higher in all cases normal in all controls and the difference was statistically significant (0.001). Moreover, RDW% decreased from

18.4% in cases to 12.7% in controls and this difference was statistically significant (P= 0.001).

Table (3) shows that the vast majority of control had normal WBCs count (96.7%), with only one case had leukocytosis (3.3%), while nearly half of the cases have leukocytosis and the difference was statistically significant (P= 0.0001). It also shows that all controls had a normal platelets count while, 30% of cases shows thrombocytopenia and the difference was statistically significant. Regarding blood culture, 88% of cases shows positive blood culture while only 6.7% of cases shows positive blood culture with a statistically significant difference (P=0.001).

Table (4) shows that RDW is statistically significant correlated with severity of neonatal sepsis. As it HB and WBCs showed no statistically significant differences with severity of the disease. On the other hand, platelets were lower among severe neonatal sepsis compared to mild forms of the disease. CRP showed a statistically significant relationship with the severity of the disease.

Table (5) shows that there was no statistically significant difference between gestational age and severity of sepsis. There was no statistically significant difference between sex and severity. Also there was no statistically significant difference between neonatal sepsis and its severity.

Table (6) shows that CRP is statistically significant increased with sever sepsis (P= 0.001), as it shows marked increase from 17.5 in mild severity to 4 folds (63.8) in severe degree, it also shows that RDW% significantly increased from 17.2% in mild degree to 19.4% in severe degree (P= 0.001).

Discussion

Neonatal sepsis is a common health care burden, practically in very-low-birth-weight infants (VLBW <1500 g), diagnosis of neonatal sepsis is not easy and difficult to be established and considered a challenge for neonatal health care providers. The gold standard method for bacterial sepsis diagnosis is blood culture. However, as pathogens in blood cultures detected only in 25% of affected patients, the sensitivity of blood culture is suspected to be low.This leads to unnecessary exposure to antibiotics before the presence of sepsis has been proven with potentially poor outcomes. Clinicians have long sought reliable markers to detect sepsis early in its course and to exclude diseases of noninfectious origin [(13)].

RDW is a parameter reflecting the heterogeneity of the peripheral red blood volume and is usually expressed with RDW-coefficient of variation (RDW-CV). In clinic, it can be understood whether the size of RBC volume is uniform through detection of RDW. The more RDW is, the more uneven the RBC size is, and the higher the volume heterogeneity is. Recent studies showed that RDW% can be taken as a “marker” of death in critical ill patients and may be used to predict death risk independently in such patients [(14)].

In this study, 48 of the cases had mild disease and the other half have severe sepsis, which reflect the high prevalence of severe sepsis and spotlights the need to diagnose this problem early to minimize its complications and burden on the health system and future development of such patients. Sepsis was more prevalent

among female cases than male and the difference was not statistically significant as shown in table (1) (P = 0.246). This finding may points to the gender inequity in health care in Assiut Governorate with more preference of male gender and less care provided to females, even in the neonatal period, as male baby is usually viewed as a precious baby from all family members, while female babies usually have low level of care. In order to remove the confounding effect of age, our findings showed that gestational age have no statistically significant relation to sepsis (P =0.81).

More than 50% of cases and controls were preterm (54% and 56% respectively), with no statistically significant difference between the two groups (P = 0.81). This reveals that cases and controls are comparable in this item so any difference in RDW or other markers between the two groups is not attributed to prematurity. Jiang et al., 2004 reported that the majority of sepsis episodes occurred in LBW (75%) and premature infants (76.7%), which may be explained by the immature host defense mechanisms and invasive life support systems in prematurity make the premature neonate particularly susceptible to overwhelming infection (Lehmann et al., 2008). Early onset neonatal sepsis (≤ 72 hours) was seen in 74% of cases while late onset was present in nearly one quarter of cases (table 1).

Blood culture remains the "gold standard" for diagnosing neonatal sepsis, even though, in many cases, it is negative. Regarding blood culture 88% of cases shows positive blood culture while only 6.7% of controls shows positive blood culture with statistically significant difference (P=0.001) (table 3). This is in agreement with results of Neal et al, 2011, who reported that as many as 60% of blood cultures would be falsely negative for common neonatal pathogens and this may be explained by the fact that maternal antibiotics given in the majority of preterm deliveries may suppress the growth of bacteria in culture and subsequently give negative blood culture results. False-negative blood cultures in apparently septic neonates may also result from insufficient blood sample taken for analysis. These limitations of using blood culture in diagnosis of neonatal sepsis arouse the need for new and effective tests for diagnosis of neonatal sepsis.

In our study, mean RDW was significantly higher in cases compared to controls(18.35± 1.79 & 12.95± 2.23 respectively) (P < 0.001), this finding is in agreement with Jianping et al, 2015 who reported that RDW value of sepsis group (19.61±1.48) was much more higher than that of normal control group (16.04±1.25), and there was a significant difference (F=15.6, P=0.0001).Increased RDW may comprehensively reflect the following pathophysiological mechanisms in occurrence and development of sepsis: First; inflammation may cause an increase of neuro-hormone and endocrine hormone in the body including noradrenaline, angiotensin 1 and other angiotensins level and renal ischemia.

These neurotransmitters can stimulate RBC proliferation through promoting the generation of erythropoietin (EPO) to result in RDW increase [(17).] Second inflammatory factors may affect bone marrow hemopoietic system and iron metabolism to cause RDW increase [(18).] Third RDW increase may indicate unstable cytomembrane which may cause multiple organ dysfunctions that make the patients' condition

deteriorate, thus leading to poor prognosis and increased mortality. Studies found that, the materials providing the nutrition to the body and cell, such as blood cholesterol, albumin and others, are lacking while RDW increases.

Therefore, increased RDW may reflect the cell membrane instability due to the lack of cholesterol and other substances in the body [19]. Fourth; severe sepsis /septic shock may be combined with multiple organ dysfunction. The study of Ping et al, 2015 [20] showed that glomerular filtration rate (GFR) decreased progressively with increasing RDW and gastrointestinal dysfunction and liver function impairment may cause dysfunction of digestion and absorption that induce megaloblastic anemia or microcytic hypochromic anemia. Therefore, increase of RDW may reflect unevenness of red cell size due to liver function impairment-induced lack of hematopoietic elements e.g., iron, folic acid, vitamin B12 in the body. Asingle or combined effect of the adverse factors above both can cause RDW increase, and RDW increase in sepsis newborns is likely caused by the combined action of several adverse factors.

Regarding other markers of diagnosing sepsis, CRP level was normal in all controls, and was elevated in all cases with statistically significant difference (P < 0.001), this finding is in agreement with Sidra et al, 2014, who founded that mean CRP level was significantly higher in patients with sepsis than controls, also in agreement with Buch et al, 2011, who reported that CRP has high sensitivity and specificity for establishing the diagnosis of neonatal sepsis which is comparable to that of blood culture results.

Serial CRP estimation may also of great value in monitoring the degree of response to treatment in clinically infected neonates and thus may guide the clinicians to estimate duration of antibiotic therapy correctly. Specificity and positive predictive value of CRP in neonatal sepsis diagnosis ranges from 93–100%. Thus, CRP can be considered as a "specific" but "late" marker of diagnosing neonatal infection. If CRP levels remain normal for long time, it correlates strongly with the absence of neonatal infection thereby guiding safe discontinuation of antibiotic therapy [22].

CBC results in our study showedthat although HB was lower in cases compared to the controls, the difference was not statistically significant (p=0.094), this may points to the multifactorial causes of low HB % other than sepsis. On the other hand, WBCs were statistically significantly (P = 0.030) higher among cases compared to normal controls, as thevast majority of controls had normal WBCs count (96.7%), while only one case had leucocytosis (3.3%). with high statistically significantdifference (p value <0.001) different. Among cases leucycytosis was seen in (48%) and leucopenia was seen in (4%). Moreover, platelet count showed a statistically significant (P < 0.001) difference between cases and controls, with many of cases showing low platelet count. All of the controls had a normal PLT count, while 30% of cases had thrombocytopenia, the difference was statistically significant (P = 0.001), this finding is in agreement with Deena et al, 2013.

A large number of studies have been performed to evaluate the use of CBC, differential count, and immature to total leukocyte ratio (I:T) for the diagnosis of neonatal sepsis. Although

the CBC has a poor predictive value, serial normal values can be used to enhance the prediction that bacterial sepsis is not present.Thrombocytopenia with counts less than 100,000 may occur in 10-60 % of neonates with sepsis, this may be attributed the cellular products of microorganisms, these cellular products cause platelet clumping and adherence leading to platelet destruction. Moreover, thrombocytopenia is generally observed after diagnosis of sepsis and usually lasts one week after diagnosis. So the presence of thrombocytopenia does not aid the diagnosis of neonatal sepsis because of the late appearance of thrombocytopenia in neonatal sepsis [(24)].

As regards severity of neonatal sepsis RDW is significantly correlated with neonatal sepsis ($P < 0.001$). It is higher in severely cases than in mild cases (19.4 ± 1.8 & 17.2± 0.58 respectively), this suggests that septic neonates with RDW ≥ 17% may have a higher severity of illness and RDW may have value in differentiating between more severe and less severe cases of neonatal sepsis, this finding is in agreement with Kader et al, 2015 who reported that incidence of RDW increase in neonatal sepsis and increased with increasingseverity of the disease. He also stated thatmean RDW value in less severe patients were 16.04 ± 0.7 and mean RDW value in more severe patients were 19.75± 1.9. This mean RDW difference in both groups was statistically significant ($P<0.001$) which points to the fact that raised RDW is associated with increasing severity of neonatal sepsis.

Link between neonatal mortality and RDW was also documented, as higher RDW is usually associated with high neonatal mortality rate, RDW was associated with 28-day mortality in patients with severe sepsis and septic shock, and there was a graded association between RDW and 28-day mortality [(26)].

HB and WBCs showed nonstatistically significant relation to the severity of the disease ($P =0.299$ and 0.129 respectively). On the other hand, platelets were lower among severe neonatal sepsis compared to mild forms of the disease (186.15± 125.95 & 284.17± 111.55 respectively) and show statistically significant relation to the severity of the disease ($P = 0.006$) . This is in agreement with Hofer et al, 2012 who reported that in VLBW infants, sepsis is frequently associated with thrombocytopenia and an elevation in mean platelet volume (MPV). However, fungal and Gram-negative pathogens are associated with a lower platelet count and more prolonged thrombocytopenia compared with Gram-positive pathogens. We conclude that common pathogens causing sepsis have different effects on platelet kinetics.

CRP showed a statistically significant relationship ($P < 0.001$) with the severity of the disease, higher in severely cases than in mild ones (63.85± 46.46 & 17.5± 9.17 respectively), this finding is in agreement with Hofer et al, 2012 who reported that CRP is higher in severe cases than in mild ones with high sensitivity and specificity in predicting neonatal Gram-negative sepsis, while IgM and IL6 are inferior to it. Arnon and Litmanovitz 2008[(28)] stated that CRP has high sensitivity and specificity for establishing the diagnosis of neonatal sepsis which may be comparable to that of blood culture results, with the added benefit of early test result availability, it is highly

recommendable that it should be used routinely in the evaluation of neonates sepsis with any features suggestive of sepsis to include or exclude the diagnosis of neonatal sepsis.

Conclusion and Recommendations

This study revealed that RDW may become a new indicator for diagnosis and risk stratification of sepsis in newborns due to being simple, less expensive, available and easily repeated as it is routinely done with CBC. Furthermore, an in-depth study of the relationship between sepsis and RDW% can make us have a better exploration of the relevant pathological mechanism from a new aspect, to look for the new treatment methods which may block the progressive development of sepsis. On the light of the above results we recommend that future studies with larger samples are needed to confirm these findings, with added emphasis on multivariable diagnostic models that incorporate other biomarkers in addition to the RDW.

Author statements :

All authors declare that the study was approved by the Institutional Ethical Committee, of faculty of medicine, Al-Azhar University and written consents were obtained from the parents, and all steps of the research take into consideration guidelines of Helsinki declaration

Authors also declare that there is no conflict of interest regarding financial or other relationships in this research. We here confirm that this work has not been published in its current form and not accepted for publication elsewhere.

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Table (1): Demographic characteristics of the studied sample

Variable	Cases=50 No. (%)	Control = 30 No. (%)	Total =80 No. (%)	Chi square (P-value)
sex:				
male	20 (40)	16 (53.3)	36 (45)	1.34
female	30 (60)	14 (46.7)	44 (55)	(0.24)
Gestational age :				
• Full term	23 (46)	13 (43.3)	36 (45)	0.05
• Preterm	27 (54)	17 (56.7)	44 (55)	(1.24)
Degree of severity:				
Mild	24 (48)	----------	----------	----------
Sever	26 (52)	----------	----------	----------
Onset of neonatal sepsis:				
Early onset	37 (74)	----------	……..	----------
Late onset	13 (26)	----------		----------

Chi square was used

Table (2): comparison between cases and control regarding hematological parameters in the studied sample

Hematological Parameters	Cases=50 Mean ± SD	Control = 30 Mean ± SD	Total =80 Mean ± SD	t-test (P-value)
Hemoglobin	14.4 ± 2.3	15.4 ± 2.5	14.9 ± 2.4	1.67 (0.08)
White blood cells	16.5± 7.3	13.2± 6.5	15.8± 6.8	2.17 (0.03)
Platelets	232.7± 127.3	377.7± 78.7	301.5± 105.4	6.2 (0.001)
C reactive protein	41.2± 15.3	2.1± 0.5	26.9 ± 6.7	9.9 (0.001)
RDW	18.4 % ± 1.8	12.7 ± 2.61	16.5± 2.1	12.4 (0.001)

t-test was used

Table (3): comparison between cases and control regarding indicators of infection in the studied sample

Variable	Cases=50 No. (%)	Control = 30 No. (%)	Total =80 No. (%)	Fisher exact (P-value)
WBCs:				
Leucopenia	2 (4)	(0)	2 (2.5)	
Normal	24 (48)	29 (96.7)	53 (66.3)	(0.0001)
Leukocytosis	24 (48)	1(3.3)	25(31.2)	
Platelets:				
• Normal	35 (70)	30 (100)	65 (81.3)	(0.001)
• Thrombocytopenia	15 (30)	0 (0)	15 (18.7)	
Blood culture:				
Positive	44 (88)	2 (6.7)	46 (57.5)	(0.0001)
Negative	6 (12)	28 (93.3)	34 (42.5)	

Fisher exact test was used

Table (4): CBC findings in mild and sever neonatal sepsis in the studied group

Variable	Mild = 24 Mean ± SD	sever = 26 Mean ± SD	Total =50 Mean ± SD	t-test (P-value)
Hemoglobin	14.8± 2.6	14.1± 2.9	14.4 ± 2.3	1.67 (0.12)
White blood cells	15.8± 5.4	17.1± 4.7	16.5± 7.3	1.29 (0.34)
Platelets	283.5± 111.5	186.6± 125.4	232.7± 127.3	5.3 (0.006)
C reactive protein	17.5 ± 9.17	63.8 ± 46.4	41.2± 15.3	9.9 (0.001)
RDW	17.2± 0.58	19.4 ± 1.8	18.4 % ± 1.8	12.4 (0.001)

t-test was used

Table (5): Relationship between degree of severity and gestational age, sex and neonatal sepsis in the studied sample

Variable	Mild = 24 No. (%)	Sever = 26 No. (%)	Total =50 No. (%)	Chi square (P-value)
Gestational age :				
Full term	12 (50)	11 (42.3)	23 (46)	0.29
Preterm	12 (50)	15 (57.7)	27 (54)	(0.58)
Sex :				
• Male	9 (37.5)	11 (42.3)	20 (40)	0.12
• Female	15 (62.5)	15 (57.7)	30 (60)	(0.72)
Neonatal sepsis:				
Early onset	18 (75)	19 (73.1)	37 (74)	0.06
Late onset	6 (25)	7 (26.9)	13 (26)	(0.84)

Chi square test was used

Table (6): RDW and CRP and its relationship with degree of severity

Variable	Mild = 24 Mean ± SD	Sever = 26 Mean ± SD	Total =50 Mean ± SD	t-test (P-value)
C reactive protein	17.5± 9.1	63.8± 12.6	43.7± 16.3	4.8 (0.001)
RDW	17.2 % ± 0.5	19.4 ± 1.8	18.3 ± 1.6	5.71 (0.001)

t-test was used