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Single CRP Measurement Vs Serial Measurements as a Predictive Value for Neonatal Sepsis

(Original Research Article)

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Abstract

Neonatal Sepsis is a clinical manifestation of bacteremia caused by microorganisms and their toxins. Diagnosis of neonatal sepsis is not easy because of unspecific signs & symptoms that may mimic other noninfectious conditions, This study is to to compare between single and serial CRP measurements; which may alter the diagnosis and management of neonates with possible sepsis. This prospective study was conducted in Neonatal department of Al-Wahda Teaching Hospital of Derna in the period from July 2020 to July 2021. This study was conducted involve 160 neonates admitted to the neonatal department with possible sepsis. The patients divided into two groups group A (n=80) for the single and group B (n=80) for the serial measurements. Serial CRP was more significant than single CRP as a marker for neonatal sepsis. Serial CRP levels are useful in the diagnostic evaluation of neonates with suspected infection. The sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy. The positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infections.

Keywords: clinical manifestation, Neonatal Sepsis, single and serial CRP, symptoms

Introduction

Neonatal Sepsis is a clinical manifestation of bacteremia caused by microorganisms and their toxins [(1)]. Diagnosis of neonatal sepsis is not easy because of unspecific signs & symptoms that may mimic other non infectious conditions [(2)].

CRP is an acute phase reactant whose level increases within 6 hours of an acute inflammation, parallels the activity of the inflammatory process, and then decreases faster than any other APR. These characteristics make CRP very useful in monitoring response to antibiotics [(3)].

Aim of the work was to compare between single and serial CRP measurements; which may alter the diagnosis and management of neonates with possible sepsis.

Methods

A **prospective study** had been conducted at the Neonatal department of Al-Wahda Teaching Hospital of Derna in the period from July 2020 to July 2021 to involve all the neonates admitted to the neonatal department with possible sepsis fulfilling the inclusion criteria.

The number of patients involved will be (**80**) for the single and (**80**) for the serial measurements with total of (**160**) patients.

The **SPSS** will be used for statistical analysis in this study.

The Inclusion criteria: Gestational Age > 33 weeks, Age of patient > 12 hrs, Both Gender, with Signs & Symptoms of Sepsis.

The Exclusion criteria: Gestational Age ≤ 33 weeks, Age of patient < 12 hrs, Associated Illnesses that rise CRP other than Sepsis like (MAS, Perinatal Asphyxia and IVH).

Samples Collection: For the SINGLE measurement; a **single** sample obtained at admission " if age > 12 hrs " or after 12 hrs of onset of S&S of sepsis. For the SERIAL measurements; **3** samples collected as follows: **CRP 0**: At Time of Admission or after 12 hrs of onset of S&S of Sepsis, **CRP 1**: Obtained 24 hrs of CRP 0, and CRP **2**: Obtained 24 hrs of CRP 1.

Results

There is no significant difference between the two studied groups as regard demographic data Table 1.

Table (1): Demographic Distribution of the Two Studied Groups.

Variable		Group (A) (n=80)	Group (B) (n=80)	t / χ^2	p
Age (days) Mean ± SD		6.21 ± 7.48	6.48 ± 7.38	.248	.825
Maternal age (years) Mean ± SD		30.42 ± 5.71	29.75 ± 4.94	.794	.429
Sex	Female	31 (38.8%)	25 (31.2%)	.989	.320
	Male	49 (61.3%)	55 (68.8%)		
Birth weight (kg) Mean ± SD		3.06 ± 0.572	2.98 ± 0.559	.895	.372
GA	**Preterm** (> 33 weeks)	19 (23.8%)	15 (18.8%)	.598	.440
	Term	61 (76.2%)	65 (81.2%)		

There is no significant difference between the two studied groups as regard diagnosis. Table 2.

Table (2): Diagnosis between the Two Studied Groups.

	Group (A) (n=80)		Group (B) (n=80)		χ^2	p
	N	%	N	%		
ABO incompatibility	7	8.8	6	7.5	17	.261
Acute cystitis	0	--	2	2.5		
Sepsis	9	11.3	10	12.5		
Mastitis	4	5	1	1.3		
Gastroenteritis	0	--	2	2.5		
Bronchopneumonia	5	6.3	4	5		
RDS	6	7.5	3	3.8		
Meningitis	8	10	9	11.3		
Pneumonia	11	13.8	16	20		
Jaundice	10	12.5	3	3.8		
Hypocalcemia	2	2.5	2	2.5		
UTI	7	8.8	13	16.3		
Omphalitis	0	--	2	2.5		
Perineal cellulitis	3	3.8	3	3.8		
Unknown	8	10	4	5		

There is no significant difference between the two studied groups as regard routine laboratory parameters Table 3.

Table (3): Routine Laboratory Parameters of the Two Studied Group

Variable	Group (A) (n=80)	Group (B) (n=80)	t	P
Hemoglobin (g/dL) Mean ± SD	11.56 ± 1.55	11.69 ± 1.46	.546	.586
TLC (10^3 /µL) Mean ± SD	10.91 ± 2.38	11.64 ± 2.51	1.89	.061
PLT (10^3 /µL) Mean ± SD	327.15 ± 67.41	316.95 ± 52.72	1.07	.288
Albumin (g/dL) Mean ± SD	3.95 ± 0.355	4.05 ± 0.444	1.57	.118
ALT (U/L) Mean ± SD	30.48 ± 7.18	28.55 ± 6.38	1.8	.074
AST (U/L) Mean ± SD	31.65 ± 6.57	30.54 ± 6.71	1.06	.292
Serum creatinine (mg/dL) Mean ± SD	0.853 ± 0.064	0.847 ± 0.072	.557	.578
BUN (mg/dL) Mean ± SD	21.78 ± 4.18	20.63 ± 4.21	1.73	.085

There is a significant difference between the two studied groups as regard single CRP Table 4**.**

Table (4): CRP of the Two Main Studied Groups

Variable	Group (A) (n=80)	Group (B) (n=80)	MW	p
CRP (mg/dL) Mean ± SD	26.1 0 - 251	39 0 - 296	**2038**	**.002**
CRP 1 (mg/dL) Mean ± SD	---	36.5 0 – 325		
CRP 2 (mg/dL) Mean ± SD	---	45 0 – 384		

There is a positive significant correlation between CRP with TLC in both groups. Table 5.

Table (5): Correlations between CRP and other Parameters in the Two Studied Groups

Variable	Group (A) (n=80)		Group (B) (n=80)	
	r	P	r	p
Age	.129	.588	.281	.230
Birth weight	.336	.147	.163	.492
Hemoglobin	.097	.684	-.009	.970
TLC	**.367**	**.025**	**.329**	**.005**
Creatinine	.011	.962	.149	.530
Albumin	-.225	.341	-.244	.132
ALT	.191	.419	.203	.390
AST	.148	.532	.374	.105

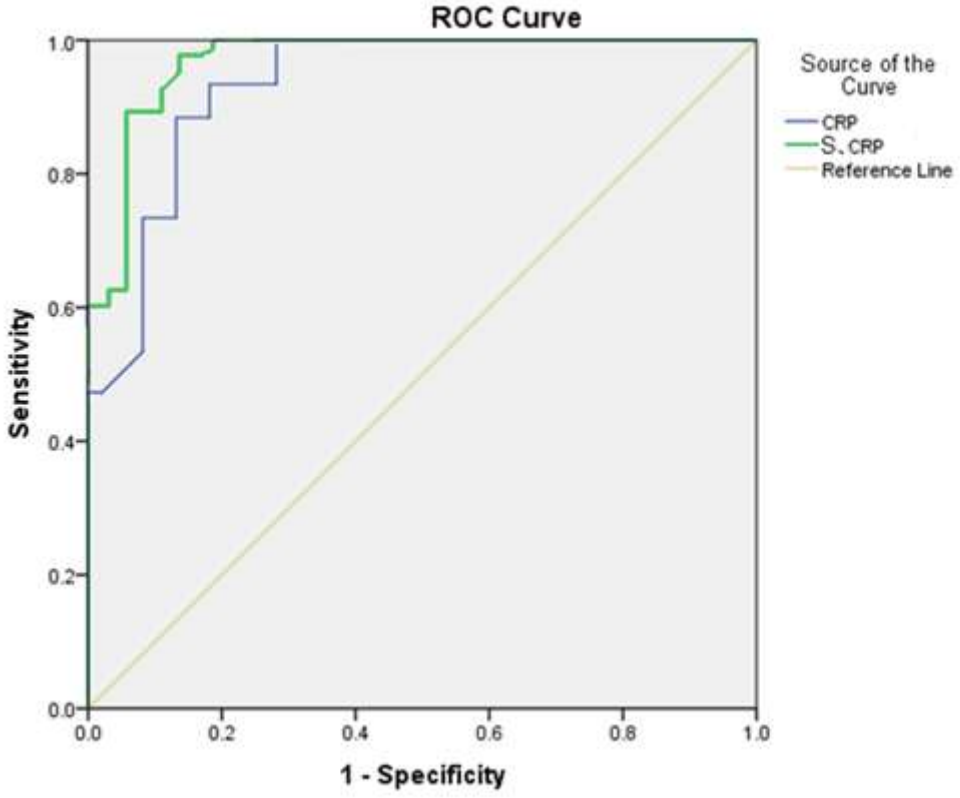

Figure 1: ROC Curve of Single CRP and Serial CRP as a Marker of Neonatal Sepsis

We found that serial CRP was more significant than single CRP as a marker for neonatal sepsis Table 6.

Table (6): Validity of CRP.

	AUC	S.E.	Sig.	95% Confidence Interval	Sensitivity	Specificity
CRP (single)	.924	.030	**.000**	.894 - 1.000	93%	79%
Serial CRP	.995	.007	**.000**	.982 - 1.000	96%	81%

Discussion

The raised of CRP concentration in septic individuals correlates well with organ failure and increases risk of death [(4)]. In the absence of methods for detecting the pathogenic bacterial agent, sepsis is diagnosed using clinical signs and increases in CRP concentrations [(5)]. CRP concentration is not affected by a prior taking of antibiotics, unlike blood culture [(6)].

The main aim of this study was to compare between single and serial CRP measurements; which may alter the diagnosis and management of neonates with possible sepsis.

This prospective study was conducted in Neonatal department of Al-Wahda Teaching Hospital of Derna in the period from July 2020 to July 2021. This study was conducted involve 160 neonates admitted to the neonatal department with possible sepsis. The patients divided into two groups group A (n=80) for the single and group B (n=80) for the serial measurements.

In the current study regarding the demographic distribution of the two studied groups, we found that there is no significant difference between the two studied groups as regard demographic data.

The present study was supported by **Sundarapandian *et al.*** [(7)] aimed to study the utility of serial CRP levels in the neonatal infection/sepsis diagnosis. Patients classified into three groups: proven sepsis (culture positive from anybody fluid), probable sepsis (culture negative but clinical and laboratory parameters suggestive of sepsis), and no sepsis (not suggestive of sepsis). Suspected infection was evaluated as early-onset (EONS, ≤72 h) in 300 neonates and late-onset (LONS, >72 h) on 150 occasions in 100 neonates. Demographics were comparable in both groups except for the age at evaluation.

Also, the study by **Valinjkar *et al.*** [(8)] aimed to assess role of CRP as a promising marker in diagnosis of neonatal sepsis and to determine the utility of CRP as a prognostic indicator in neonatal sepsis. The study enrolled 200 neonates with signs and symptoms of neonatal sepsis. 117 (58%) neonates were male and 83 (42%) neonates were female. Of these 200 neonates 143 (72%) neonates are vaginally delivered &57 (28%) neonates delivered by LSCS.

Regarding Diagnosis between the two studied groups, we found that there is no significant difference between the two studied groups as regard diagnosis.

The study by **Sundarapandian *et al.*** [7] revealed that There were 38 episodes of proven sepsis (EONS=18, LONS=20), 62 of probable sepsis (EONS=44 and LONS=18), and 350 of no sepsis. Organisms were isolated from 25 blood cultures (EONS=11 and LONS=14), 6 urine cultures (3 each in EONS and LONS), and no CSF cultures. Blood and urine culture isolated the same organism in two cases each of EONS and LONS. Staphylococcus epidermidis (coagulase-negative staphylococci) was isolated from blood culture in two cases of EONS and three cases of LONS. Of these five cultures, sepsis screen was abnormal in one case. Klebsiella pneumoniae was the most frequently isolated organism in EONS and Escherichia coli and Staphylococcus aureus in LONS. In EONS, proven sepsis was less common and probable sepsis was more common, vice versa was observed in LONS. Although CSF culture was negative in all the cases, the cell counts, glucose, and protein levels were abnormal in one case of EONS and four cases of LONS suggesting the fact that meningitis is probably a common occurrence in LONS.

However, **Mkony *et al.*** [9] revealed that 67.3% of the participants had fever, 38.9% low muscle tone, and 79.8% were found to have fast breathing. A positive blood culture was found in 40 (19.2%) of the 208 blood samples. The bacteria isolated included Klebsiella spp 14 (35%), E. coli 12 (22.5%), CoNS 9 (30%), S.aureas 4 (10%), and Pseudomonas aeroginosa 1 (2.5%).

Furthermore, the study by **Yaseen *et al.*** [10] regarding signs and symptoms reported that refusal to feed was a complaint in more than 90% of both groups (sepsis and no sepsis). Lethargy was less frequent among cases with sepsis (82.7%) compared to 95.5% of cases without sepsis, the difference was statistically significant. Seizure was reported in 12.5% of cases with sepsis compared to only 4.3% of no sepsis group, the difference was significant (p=0.039). No significant difference between the two groups was observed regarding other symptoms. Tachypnea was the most frequent sign in both groups (37.5% and 44.6% respectively). Fever was observed in about 10% of both groups. No statistical differences have been observed between the two groups regarding any sign.

Regarding the routine laboratory parameters of the two studied group, we found that there is no significant difference between the two studied groups as regard routine laboratory parameters.

Many attempts have been made to develop a set of screening tests, which can rapidly diagnose infected neonates, thus, preventing delay [11]**.** The diagnosis based on culture of blood, cerebrospinal fluid or urine is established after delay of 24 hours. However, many patients with bacterial infection have negative blood cultures [12]. It has been suggested that a combination of hematological tests (total leucocyte count (TLC), absolute neutrophil count (ANC), immature to total neutrophil ratio(I/T ratio), platelet count and C-reactive protein (CRP) estimation provide early diagnosis of bacteremia. [13]

The study by **Arif *et al.*** [14] reported that the combination of TLC, ANC and CRP is more sensitive in detection of culture positive than culture negative cases of neonatal sepsis.

Also, the study by **Choo *et al.*** [15] revealed that the incidence of neonatal sepsis was non significantly correlated to the WBC and Platelet count but significantly correlated with ANC.

Regarding the CRP of the two main studied groups our results showed that there is a significant difference between the two studied groups as regard single CRP. And we found that there is a positive significant correlation between CRP with TLC in both groups.

This was in agreement with the study by **Arif *et al.*** [14] who reported that there was positive significant correlation between CRP with TLC.

Similarly, **Ahmed *et al.*** [16] revealed that TLC was significantly correlated with CRP and concluded that a set of investigations including CRP, TLC, ANC, thrombocytopenia, cytoplasmic vacuolization in the neutrophils and GAC for polymorphs are highly sensitive in detection of culture negative cases of neonatal sepsis. Moreover, a combination of three tests enhances the sensitivity of these tests.

To test the validity of single and serial CRP we used ROC curve analysis of single CRP and serial CRP as a marker of neonatal sepsis. And we found that We found that serial CRP was more significant than single CRP as a marker for neonatal sepsis.

Our results were in agreement with **Sundarapandian *et al.*** [7] who revealed that there was a strong correlation between the diagnoses of proven or probable sepsis and elevated CRP levels (≥1.0 mg/dl), for both early- and LONS episodes, supporting the diagnostic utility of CRP. The sensitivity of CRP 2 was > CRP 1, but maximum sensitivity was achieved by CRP 3 level only. A CRP level has a much higher predictive value in ruling out than ruling in neonatal infection/sepsis (reaching almost 99-100% for both sepsis types). So, they concluded that Serial CRP measurements are useful in the diagnosis of neonatal infection/sepsis.

This was supported by **Valinjkar *et al.*** [8] who reported that Negative predictive value of SERIAL CRP increases from 35% on day 1 to 94% on day 10 / or on discharge, which signifies that serial CRP value rules out sepsis with high accuracy and helpful in deciding duration of antibiotics in neonatal sepsis. Sensitivity of SERIAL CRP increases from 31% on day 1 to 53% on day10 / or on discharge which is significant. And they concluded that CRP is the rapid diagnostic test which has high sensitivity and negative predictive values in diagnosis of neonatal sepsis.

Also, the study by **Mkony *et al.*** [9] revealed that Single CRP in combination with Rubarth's newborn scale of sepsis can be used for rapid identification of neonates with sepsis due to high sensitivity (95.6%) but cannot exclude those without sepsis due to low specificity (56.4%). Serial CRP done 12hrs apart can be used to exclude

non-cases. This study demonstrated very high levels of resistance to the first-line antibiotics.

Our results were also in agreement with **Benitz *et al.*** [17] as they concluded that serial CRP was more significant than single CRP as a marker for neonatal sepsis.

Conclusion

Serial CRP levels are useful in the diagnostic evaluation of neonates with suspected infection. The sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy. The positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infections.

Declarations

Consent for Publication: I confirm that all authors accept the manuscript for submission

Availability of Data and Material: Available.
Competing Interests: None

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