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Contribution of C-reactive protein in the detection of sepsis in newborns: A cross-sectional study

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Abstract

Background: The objective of our study is to evaluate the effectiveness and contribution of the C-reactive protein dosage, widely used in our context, in the early detection of neonatal sepsis and diagnostic orientation.

Methods: Retrospective study, conducted at the clinical biochemistry laboratory, in collaboration with the microbiology laboratory, in newborns admitted to the neonatology department for management of confirmed or suspected neonatal infection, during a period extending from January to December 2020.

Results: A total of 300 blood cultures were performed. The sex ratio M/F: 1,38. The average age was 11.24 days. There were 148 positive cultures among which there were 120 positive CRP, that is 81%. And 152 sterile cultures with 50 positive CRP. The mean CRP value in the positive cultures was 62.67 mg/L. It was 15.53 mg/l in sterile cultures. The chi-square statistic calculated for our analysis is 70.906 with a significance level (alpha) of 0.05. The point-biserial correlation coefficient (r_pb) for this study is 1.51

Conclusion: Although there are currently more specific and sensitive early markers of inflammation, the C-reactive protein determination, widely used in our context, provides sufficient sensitivity and specificity in the diagnostic orientation of neonatal sepsis.

Keywords: C-reactive protein; Screening; Biomarkers; Newborns; Septicemia

1. Introduction

Neonatal sepsis is an invasive infection, usually bacterial, occurring during the neonatal period. It is responsible for 13% of neonatal mortality, after prematurity and intrapartum complications. This high mortality is due, among other things, to the diagnostic difficulty of neonatal sepsis, which presents with multiple and non-specific symptoms: decreased spontaneous activity, feeding difficulties, apnea, bradycardia, thermal instability, respiratory distress, vomiting, diarrhea, abdominal distension, nervousness, convulsions, and jaundice[1-3.]

The gold standard in the diagnosis of neonatal sepsis is the isolation of the causative organisms in blood cultures. However, this method requires an incubation and completion time that can take several days, with the possibility of isolating a germ in only 40 to 50% of cases. This makes it necessary to measure early markers of infection with good

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specificity and sensitivity. Several markers are used in this sense, the rate of leukocytes, neutrophils, C-reactive protein, pro-calcitonin, interleukin 6, etc., and constitute a screening method that can guide the management [4].

The objective of our study is to evaluate the effectiveness and contribution of the C-reactive protein dosage, widely used in our context, in the early detection of neonatal sepsis and the diagnostic orientation of the clinician while waiting for the confirmation of the microbiologist. On one side, for the initiation of early antibiotic treatment and on the other side, to avoid an abusive antibiotic treatment which can disturb the commensal flora of the newborns and amplify the emergence of bacterial resistances.

2. Materials and methods

This is a retrospective study, conducted at the clinical biochemistry laboratory of the Mohamed VI University Hospital Center of Marrakech, in collaboration with the microbiology laboratory, in newborns admitted to the neonatology department for management of confirmed or suspected neonatal infection, during a period extending from January 2020 to December 2020.

All newborns aged less than 28 days who had a C-reactive protein test performed within 5 days of the date of blood culture collection (5 days being the maximum time for the return of blood culture results) were included in the study

Each blood culture was incubated at 37°C in the BD BACTEC automated system. The identifications and antibiograms were carried out by PHOENIX M50 and the interpretation was made according to the standards of the Antibiogram Committee of the French Society of Microbiology (CA-SFM/EUCAST)

Blood cultures positive for commensal bacteria (coagulase-negative Staphylococcus SCN, Corynebacteria spp, and Bacillus spp) were excluded from the study.

Quantitative determination of C-reactive protein (CRP) by photometric method (immunoturbidimetry) using the Roche Cobas 6000 automated system was performed in the Clinical Biochemistry Laboratory.

A threshold value of C-reactive protein higher than 6mg/l was considered positive.

Data collection included sex, age, identified germs, CRP value, and the presence or absence of multidrug-resistant bacteria.

Data and statistical analysis were performed using Excel software. The different values were calculated according to the following formulas:

- Sensitivity= True positives/ (True positives + False negatives) X 100,
- Specificity = True negatives/ (True negatives + False positives) X 100,
- Positive predictive value = True positives/True positives + False positives
- Negative predictive value = True negatives/True negatives + False negatives

The sensitivity, specificity, positive predictive value, and negative predictive value were calculated for CRP in comparison to blood culture. The association between CRP levels and blood culture results was determined using:

The Chi-square (X2) test, calculated using this formula:$\chi^2 = \Sigma [(O - E)^2 / E]$. A p-value < 0.05 for Chi-square test (X2) was considered to be statistically significant.

The point-biserial correlation coefficient (r_pb), calculated based on the means, standard deviations, and the total number of values for the two groups (Positive cultures and negative cultures)) using this formula: $r_{pb} = (\bar{X}_1 - \bar{X}_0) / [\sigma(\text{Group Positive cultures}) * \sigma(\text{Group Negative cultures})]$

3. Results

Of a total of 300 blood cultures performed, there were 126 female and 174 male newborns, The sex ratio M/F: 1,38

The average age was 11.24 days

There were 148 positive cultures among which there were 120 positive CRP, that is 81%. And 152 sterile cultures with 50 positive CRP.

Among the positive cultures, there were 145 late neonatal infections and 3 cases of early neonatal infection (<72h)

The mean CRP value in the positive cultures was 62.67 mg/L. It was 15.53 mg/l in sterile cultures.

Table 1 Comparison between culture and c-reactive protein dosage

Variables	Growth in Blood cultures	No Growth in Blood cultures	Total
Reactive CRP	120	50	170
Mean value(mg/l)	76.83	44.38	67.28
Non reactive CRP	28	102	130
Total	148	152	300

Table 2 Predictive values of CRP in patients with neonatal septicemia

Parameters	Value (%)
Sensibility	81
Specificity	67.1
Positive predictive value	70.5
Negative predictive value	78,4
Diagnostic accuracy	81.09

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Table 3 Mean value of CRP in relation to organisms isolated in patients with neonatal septicemia

Isolated organisms	Blood culture positive (n=148)	Reactive CRP (n=120)	% of CRP positivity	Mean value (mg/l)
Gram negative bacteria	118	103	87.2%	79.55
Gram positive bacteria	30	17	56.6%	62.5

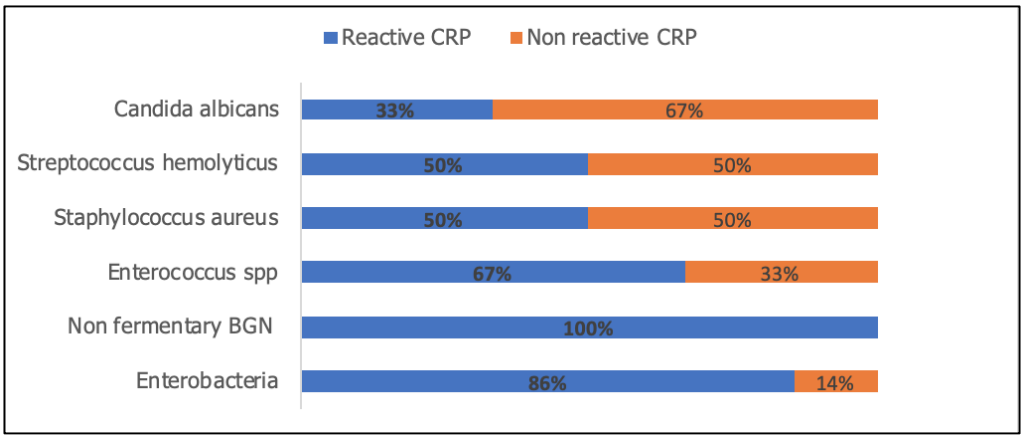

Figure 1 CRP positivity according to bacterial groups

Regarding CRP values according to the presence or not of multi-antibiotic resistance, there were 79 (53,7%) multi-resistant bacteria isolated in the blood cultures for which there was 91,1% of CRP positives and a mean value of 67,6 mg/l. Versus 69 (46,3%) non-multi-resistant drug bacteria of which there was a percentage of 69,5% CRP positive and a mean value of 59,5 mg/l

The chi-square statistic calculated for our analysis is 70.906 with a significance level (alpha) of 0.05

The point-biserial correlation coefficient (r_pb) for this study is 1.51

4. Discussion

Initially Discovered in 1930 by Tillett and Francis, C-reactive protein (CRP) was isolated from sera of patients infected with *Streptococcus pneumoniae* with which it reacts through the C polysaccharide contained in the wall.[6]

Forty years later, Volanakis and Kaplan identified the specific ligand for CRP in the pneumococcal C-polysaccharide as phosphocholine, part of the techoic acid in the pneumococcal cell wall (7). Although phosphocholine was the first ligand defined for CRP, a number of other ligands have since been identified. In addition to interacting with various ligands, CRP can activate the classical complement pathway, stimulate phagocytosis, and bind to immunoglobulin receptors (Fc R).[8]

The gene encoding CRP synthesis is located on chromosome 1 and approximately 35-40% of the variability in CRP concentration between different healthy individuals is due to genetic polymorphisms [9-10]. Plasma CRP is mainly produced by hepatocytes and regulated by the cytokines interleukin-6 (IL-6), and to a lesser extent by IL-1β and tumor necrosis factor-α9. Although extrahepatic synthesis of CRP has also been reported in neurons, atherosclerotic plaques, monocytes, and lymphocytes, the liver is the only site of CRP elimination. Thus, plasma concentrations of CRP are almost solely determined by the synthetic rate of its production in the liver [11], Its plasma half-life is approximately 19 hours.[12]

In 1981, Shine et al [13] evaluated the concentration of CRP by radioimmunoassay in 468 sera of apparently healthy adult volunteer blood donors and reported a median concentration of 0.8 mg/L. More recently, Rifai and Ridker [14] used three high-sensitivity techniques to determine CRP distributions in their cohort of 22,000 healthy adults in the United States. The median CRP values for men and women were 1.5 and 1.52 mg/L, respectively. Similarly, Imhof et al [15] measured CRP values in 13,000 apparently healthy subjects from different populations in Europe. The median concentration reported in individual cohorts ranged from 0.6 to 1.7 mg/L. [16]

During the acute phase of inflammation, the hepatic synthesis of CRP increases within a few hours and can reach 1000 times normal [17-18]. The level remains elevated as long as the inflammation or tissue damage persists and then decreases rapidly.

Any elevation of serum CRP in the newborn represents endogenous synthesis, as maternal passage across the placenta is extremely low [19]. De novo hepatic synthesis starts very rapidly after stimulus with serum concentrations exceeding 5 mg/L in about 6 h with a peak around 48 h [20].

The determination of CRP is performed by immunonephelometry or immunoturbidimetry: Erythrocytes from capillary and venous whole blood are separated from plasma by centrifugation. The plasma is then diluted with HEPES buffer and transferred to the reaction chamber where it is mixed with the anti-CRP antibody reagent on latex. The CRP in the diluted plasma binds to the anti-CRP antibody on the latex particle. The concentration of CRP is calculated from the change in absorbance measured at 525 nm and 625 nm which is related to the degree of agglutination.[21-22]

In this study, there was a male predominance, with a sex ratio of 1.38, and a mean age of 11.24 days. This result is consistent with the local [23-24], national [25], and international [26-28] literature.

There were 120 positive CRPs for 148 positive cultures, i.e. a positivity rate of 81%, which is comparable to the results in the literature, which are 91% and 85% respectively (29)(26).

Regarding sensitivity, this study agrees with the literature, with variations of +/- 10%. And it is higher than the specificity in this study, as well as in the literature.

The specificity is 67% in this study, it is an average compared to the different values calculated in the literature [4] [26-29], but it is consistent with the meta-analyses [30-31].

The positive and negative predictive values are comparable to the data in the literature. (Table 4)

Table 4 Positive and negative values in the literature

Study	Sensibility	Specificity	Positive predictive value	Negative predictive value	Diagnostic accuracy
Our study	81	67	70	78.4	81
N. Monga et al.(26)	85	43.4	57.14	76	63
Y. Goswami et al.(29)	91	94	91.2	-	-
E. Hisamuddin et al.(27)	76.9	53.4	80	48.9	70
S. Younis et al.(28)	97.3	95.2	97.3	95	-
R. Kumar et al(4)	90	96	95	-	-
Xu. L et al. (Métanalyse)(30)	69	77	-	-	-
Milcent. K et al (32)	75	75	-	-	-

The CRP positivity rate is influenced by the pathogenic bacterial family, it was more increased in infections by Gram-negative bacteria (87.2%), reaching 100% for non-fermentative BGN and 86% for Enterobacteriaceae, compared to Gram-positive bacteria where it was 56.6%. The same is true for the mean CRP value, which was 79.55 mg/l for BGN infections versus 62.5 mg/l for GMP. This result is consistent with the literature [26][33].

As part of our retrospective study aimed at assessing the contribution of CRP (C-reactive protein) measurement in predicting sepsis in newborns, we conducted a statistical analysis using the chi-square test. Our sample consisted of 300 patients.

The chi-square statistic calculated for our analysis is 70.906 with a significance level (alpha) of 0.05. The degrees of freedom (df) for this analysis are 1, as we used a 2x2 contingency table to compare CRP measurement results with the presence of sepsis.

By comparing the calculated chi-square statistic with the critical value corresponding to a significance level of 0.05, we observe that the calculated chi-square statistic is greater than the critical value. Therefore, we reject the null hypothesis.

This result indicates a statistically significant association between CRP measurement and the presence of sepsis in newborns in our sample. In other words, our analysis suggests that CRP measurement is potentially useful for predicting sepsis in newborns.

However, it is important to note that further analyses and studies are needed to assess in more detail the strength of this association and its clinical validity. Additionally, it is worth highlighting that our analysis was conducted with a significance level of 0.05, meaning we accepted a 5% risk of Type I error. Therefore, further research may be required to confirm these results and evaluate their clinical applicability.

The point-biserial correlation coefficient (r_pb) for this study is 1.51. The point-biserial correlation coefficient ranges from -1 to 1, where 1 indicates a strong positive correlation between the binary variable (presence/absence of sepsis) and the quantitative variable (CRP levels). This means there is a strong positive relationship between the presence of sepsis and CRP levels in this study.

5. Conclusion

Although there are currently more specific and sensitive early markers of inflammation, the C-reactive protein determination, widely used in our context, provides sufficient sensitivity and specificity in the diagnostic orientation of neonatal sepsis, and also in the implementation of early probabilistic treatment before the result of blood culture in order to reduce the mortality and morbidity rate related to diagnostic delay.

The statistical analysis highlights the significance of the study while emphasizing the need for further research to better understand the clinical relevance of the association between CRP measurement and sepsis in newborns.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest / Competing interests

Statement of informed consent

Since the study is only based on anonymous Laboratory Data. No consent was needed.

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