Original Research Article

Diagnostic utility of C reactive protein and widal test with hematological parameters for sepsis in children attending a tertiary care hospital, South India

Dhananjaya C.D.[1], Sunil B.N. [2]

[1]Dr. Dhananjaya C.D., Associate Professor, Department of Pediatrics, The Oxford Medical College & Research Centre, Bengaluru, [2]Dr. Sunil B.N., Assistant Professor, Department of Community Medicine, Sri Devaraj Urs Medical College, Kolar, Karnataka, India.

Corresponding Author: Dr. Sunil B.N., Assistant Professor, Department of Community Medicine, Sri Devaraj Urs Medical College, Kolar, Karnataka, India. E-mail: dravidbage@gmail.com

Abstract

Background: Sepsis is a major problem in Children and Clinical criteria alone could not establish the diagnosis of childhood sepsis. It is extremely important to make an early diagnosis of sepsis for the prompt institution of anti-microbial therapy, which improves outcomes. **Objective:** The aim of this study is to determine the diagnostic utility of C - reactive protein (CRP) in combination with hematological parameters of CBC as early diagnostic marker in detection infections in children. **Methodology:** This prospective study was conducted on children attending pediatric OPD or admitted as inpatient at Oxford Medical College Hospital, Bengaluru, Karnataka. Blood specimens were obtained from each child prior to commencement of antibiotics for sepsis work up and subjected to CBC, CRP and Widal test. **Results:** 274 (54.4%) out of 503 children were boys and majority 77.9% of the study population were belonging to Under 5 age group. The mean difference observed between the groups of CRP positive and negative children for all the components of the Complete Blood Count was statistically significant except for Monocytes and Eosinophils which tells that these variables were significant predictors of sepsis in the children. **Conclusion:** The combination of total WBC count along with CRP could be a reliable diagnostic tool to detect the presence of Infections in children. Routine ordering of CRP for detection of Infection in febrile children will increase the probability of correct diagnosis and help the pediatrician in more accurate and effective management of sepsis in children.

Keywords: Sepsis, CRP, CBC, Children

Introduction

Fever in children is one of the most common reasons for parents to seek medical care which accounts to approximately 20% of all the cases in Pediatrics [1]. Children may present with fever as an initial/isolated symptom of a yet undifferentiated illness or with localizing signs that suggest an etiology such as pneumonia.

A majority of children with fever without localizing signs will have a viral etiology which does not warrant laboratory evaluation and can often be managed with instructions for ensuring adequate hydration and use of antipyretics [2].

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In one study it is estimated that up to 10% of febrile children, especially those 3 months of age and younger will have bacterial illnesses in the form of occult bacteremia, septicemia, bacterial meningitis, pneumonia, UTI, bacterial gastroenteritis, osteomyelitis, septic arthritis, and other general endemic tropical diseases [3].

However, etiologies of fever in the Indian context could vary from benign viral illnesses, commonly reported in US and Europe (e.g.respiratory syncytial virus (RSV), Enterovirus infections) to illnesses by organisms uncommon in industrialized countries: bacteria (e.g. *S. typhi*), viruses (*e.g.* measles, dengue, chikungunya) and parasites (e.g.malaria, kala azar) as well as endemic illness outbreaks due to meningococci and leptospira.

India is a tropical country with a distinct spectrum of common tropical illnesses particularly seen in post monsoon season such as dengue, rickettsial infections, scrub typhus, malaria (usually due to Plasmodium falciparum), typhoid and leptospirosis [4].

Development of a consensus statement that is relevant to the epidemiology of illness in the Indian context will help reduce practice pattern variation, optimize resource allocation as well as education, training and decision making by both policy makers and health care administrators in the federal, public and private sectors. Moreover, evaluation and management of the febrile child, continues to remain a clinical challenge in the Indian context and the development of a consensus based practice guideline will serve as a valuable resource.

C-Reactive Protein (CRP) is an acute phase protein primarily synthesized in the liver [5]. In response to an inflammatory stimulus, the CRP levels rise up to 50,000 times above normal, typically within 6 hrs and peak at 48 hours [6]. CRP is known to activate the classical complement cascade, stimulates phagocytic cells for phagocytosis [7]. In any infection, CRP secretion is induced by pro-inflammatory cytokines that are secreted by host mononuclear cells [8].

Though the primary function of CRP is conjugating pathogens and inducing their destruction byhost complement system [9], its sustained release can also have adverse effects [10,11]. It is postulatedthat prolonged increased CRP levels could contribute to an imbalance in inflammatory response leading to a reduced control of parasitemia[12,13].

In this study, authors intended to determine
i) The C-reactive protein (CRP) levels in Children suffering from fever
ii) The relationship between CRP and the Hematological parameters in CBC and
iii) The usefulness of CRP in combination with CBC as a2 Significant Predictor of Illness in Children.

Objectives- To determine the diagnostic utility of CRP and Widal test with Haematological Parameters for Sepsis in Children attending a tertiary care hospital

Materials and Methods

Study design and Site: The present study is a Hospital based cross-sectional study which was carried out among the Children who presented to the Paediatric OPD or Inpatients attending Oxford Medical College Hospital and Research which is a tertiary care hospital in Bengaluru, Karnataka.

Duration of study: 1 year (May 2018 and April 2019)

Study population: All the Children who presented to paediatric OPD or admitted to Paediatric ward with history suggestive of Infection were included in the study.

Inclusion criteria
- 0 to 19 years age of either sex
- High suspicion of Infection in the Child by Clinician

Exclusion criteria
- Seriously ill Children
- Children already started on Antibiotics
- Not willing to take part

Sample size and sampling method: Assuming that 50% of them will have some evidence of Infection by means of CBC, CRP and Widal and with absolute precision of 6% and with two sided confidence interval of 95%, the minimum sample size was calculated to be 278. Consecutive sampling strategy was adopted till the sample size is completed.

Study tool and variables: A pretested semi-structured questionnaire which included socio-demographic details, duration and type of illness and clinical features. Venous blood was drawn from all the children fulfilling Inclusion Criteria at the time of admission or at the time of Outpatient consultation.

Specimens and tests which were performed: The specimens of blood were obtained from each child prior to the commencement of the antibiotics for the sepsis work up, which included hematological parameters like the hemoglobin, total leukocyte count, packed cell volume, monocyte, neutrophil and eosinophil count, platelet count and red blood count. All the blood samples were simultaneously subjected to C-reactive protein (CRP) estimation and Widal test and the test results were obtained from the Laboratory.

Statistical analyses: Data were entered in Excel and analysis was done using SPSS version 22. Descriptive statistics were represented as frequencies, percentages, mean and standard deviation. Anova was used to find the difference between the groups.p value was considered statistically significant if it was less than 0.05.

Ethical considerations: A written informed consent was obtained from all the study participants. All the collected information was kept confidential, and is being used for research purpose only.

Results

The study included 503 children attending pediatric OPD / Inpatients whose age ranged from birth to 17 years. Majority of the children 389 (77.2 %) belonged to Under 5 age group. (Table 1) Out of 503, 274 (54.4%) were boys and 229 (45.6%) were girls.

Table-1: Distribution of children as per the Age Group

Age	Number	Percentage
< 1 year	17	3.3
1 – 5 year	372	73.9
6 – 10 year	100	19.8
11 – 17 year	14	2.7
Total	**503**	**100**

Table-2: Descriptive statistics of the continuous variables used in the study

Variables	Minimum	Maximum	Mean	Std. Deviation
Age (in Years)	< 1	17	4.12	2.73
HB% (gm %)	6.90	16.80	12.09	1.31
PCV	25.10	47.20	36.42	3.15
TLC (thousands/dl)	1.14	36.80	9.16	5.04
Neutrophils	5	88	52.77	16.51
Lymphocytes	5	91	38.86	16.28
Monocytes	2	63	5.03	2.93
Eosinophils	1	8	3.58	1.16
RBC (million/dl)	3.14	6.90	4.71	0.43
PLT (lakhs/dl)	0.32	9.89	3.20	1.34

*HB- Hemoglobin, PCV- Packed Cell Volume, TLC – Total Leukocyte Count, RBC – Red Blood Cell, PLT – Platelet Count

Table 2 shows the descriptive statistics ie, Range, Mean and Standard deviation of Age, Hemoglobin, Packed Cell Volume, Total leucocyte count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Red Blood Cells and Platelet Count. The mean values of all the children were within normal limits.

Table-3: Comparison of Mean and Standard deviation of various Investigations between Widal Positive and Negative Reports

Widal test		HB%	PCV	TLC	N	L	M	E	RBC	PLT
Negative (406)	Mean	12.07	36.11	9.34	53.05	38.50	4.93	3.65	4.70	3.27
	Std. Deviation	1.32	3.14	5.21	16.22	15.94	1.46	1.15	0.42	1.36
Positive (97)	Mean	12.16	37.67	8.42	51.56	40.37	5.45	3.27	4.73	2.92
	Std. Deviation	1.25	2.90	4.21	17.73	17.64	5.98	1.13	0.46	1.26
Total (503)	Mean	12.09	36.42	9.16	52.77	38.86	5.03	3.58	4.71	3.20
	Std. Deviation	1.31	3.154	5.04	16.51	16.28	2.93	1.16	0.43	1.34
*p value		0.580	**< .001**	0.108	0.423	0.310	0.114	**0.004**	0.600	**0.021**

*Anova

All the children underwent Widal test and 97 out of 503 were positive for it. The mean difference of all the components of Complete Blood Count was compared between Widal positive and negative children. It was observed that, there was mean difference observed between the groups of Widal positive children and Widal negative children for all the components of the Complete Blood Count and it was statistically significant for Packed Cell Volume, Eosinophil Count and Platelet Count. So these three components of Complete Blood Count were significant predictors of Typhoid in the study Children (Table 3).

Table-4: Comparison of Mean and Standard deviation of various Investigations between CRP Positive and Negative Reports

CRP		HB%	PCV	TLC	N	L	M	E	RBC	PLT
Negative (325)	Mean	12.22	36.86	7.71	49.31	42.30	5.10	3.59	4.74	2.97
	Std. Deviation	1.36	3.22	4.06	16.56	16.45	3.58	1.16	0.44	1.18
Positive (178)	Mean	11.85	35.60	11.81	59.07	32.57	4.90	3.54	4.65	3.63
	Std. Deviation	1.18	2.85	5.57	14.48	13.96	.99	1.15	0.41	1.51
Total(503)	Mean	12.09	36.42	9.16	52.77	38.86	5.03	3.58	4.71	3.20
	Std. Deviation	1.31	3.15	5.04	16.51	16.28	2.93	1.16	0.43	1.34
*p value		0.002	<0.001	<0.001	<0.001	<0.001	0.479	0.652	0.023	<0.001

*Anova

All the children blood sample was subjected to CRP testing and 178 out of 503 were positive for it. The mean difference of all the components of Complete Blood Count was compared between CRP positive and negative children. It was observed that, there was mean difference observed between the groups of CRP positive children and CRP negative children for all the components of the Complete Blood Count and it was statistically significant for all its components except Monocytes and Eosinophils. So all the variables were significant predictors of Infection in the body (Table 4)

Discussion

Sepsis which has high mortality rate, still remains a diagnostic and treatment challenge for the pediatricians. An early diagnosis of childhood septicemia helps the clinician in instituting antibiotic therapy at the earliest, thereby reducing the complications and mortality in the children. An early identification of an infected child also helps in avoiding the unnecessary treatment of a non-infected one. The blood culture not only takes time, but it is also complicated, with a low yield. The readily achievable complete blood count and the leukocyte differential counts have a relatively poor specificity for diagnosing sepsis. Therefore, the need persists for improved diagnostic indicators of sepsis in childhood.

Pulliam PN et al., demonstrated that CRP performs better in predicting severe Bacterial Infection in febrile children less than 36 months of age compared to leukocyte and neutrophil count [14]. Andreola B et al., demonstrated that CRP has a superior discriminatory power to total and differential WBC in detecting serious Bacterial Infection in children with fever without a source as it is more sensitive and specific [15]. The same results concerning the CRP and procalcitonin value in evaluating young children with bacterial or viral infection were demonstrated by the study of Olaciregui I et al [16].

In a recent study Kossiva L et al., evaluated the parameters complete blood count in combination with CRP and ESR to distinguish the presence from the absence of infection [17]. In the current study, CRP has a better discriminatory power with higher sensitivity and specificity as compared to WBC. In this study, a strong inverse relationship between increased CRP levels and decreased hemoglobin and RBC levels was observed. Acute plasma proteins are synthesized by hepatocyte cells in the liver and it was also shown that liver as the site of CRP formation which was consistent with the other study [5].

As the sensitivity and the specificity of the individual tests may not justify their individual use in newborn infants and children, a significant improvement of diagnostic capability when used in various combinations, has been studied. An above 80% sensitivity by the combination of any 2 or more positive tests in culture positive Early Onset sepsis was also reported earlier from Indian studies [18]. In a study done at tertiary care hospital at Udaipur where both CRP and Hematological parameters were done for all the children, the sensitivity of the hematological screening parameters and CRP varied from 73.03-92.30% [19].

In a study done at Mangaluruto find out the relationship of CRP with Hematological parameters in Malaria Patients, a highly significant positive correlation was found between increase in parasitemia and C-reactive protein levels in *P.falciparum*and *P. vivax*patients. While a significant positive correlation was observed between the increased parasitemia (%) and CRP levels, a significant negative correlation was observed between CRP and decreased hemoglobin, RBC, platelets and across various infecting species [20].

Limitations- Only one serum sample was available for CRP testing. Serial CRP levels in these patients would have been more helpful as a single CRP gives a probability but not a certainty of presence or absence of serious bacterial infection.

Conclusion

In conclusion, the findings of the present study confirm that the serum levels of CRP in combination with WBC counts and other hematological parameters are better indicators of infection in the early diagnosis of sepsis in childhood than isolated use of CBC and it also aids in the evaluation of the response of the disease to the antibiotic therapy. The benefit of measuring serum CRP routinely in the diagnosis and follow-up of sepsis, is that it reduces the hospital costs. Such a benefit might support a wider acceptance of the test along with CBC in the routine practice.

Hence, the combination of total WBC count along with CRP could be a reliable diagnostic tool to detect the presence of Bacterial Infections in children. Routine ordering of CRP for detection of Bacterial Infection in febrile children is reasonably acceptable but further comparison of the performance of other diagnostic markers will be more meaningful to infer the diagnostic criteria for Bacterial Infection among children.

New Knowledge- It is very difficult to diagnose the children with sepsis based on clinical features. The common investigation done to rule out sepsis in children is CRP. But CRP alone will not be enough to make accurate diagnosis. Hence addition of Hematological Parameters with CRP will increase the probability of accurate diagnosis of sepsis in Children.

Authors Contribution

Dr. Dhananjaya C.D: The principal investigator was involved in protocol writing, data collection and manuscript preparation.

Dr. Sunil B.N: Corresponding author was involved in protocol writing, data analysis and manuscript editing.

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