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Original Article

Pharmacology Section

Role of C-reactive Protein in Acute Respiratory Tract Infections in Children

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ABSTRACT

Introduction: C-reactive Protein (CRP) is an acute phase protein synthesised in liver. Its production is mainly by Interleukin 6, Interleukin 1β and tumor necrosis factor in response to infection or tissue inflammation. Raised CRP levels are considered as a marker of inflammation. Therefore, they can be used for screening of inflammatory conditions or other disease activity.

Rapid increase in the synthesis of CRP within hours, after tissue injury or infection suggests that it contributes in host defense and that it is a part of the innate immune response. CRP plays an important role in host's defense against infections.

Aim: To measure CRP levels qualitatively and semi quantatively in Paediatric patients with Acute Respiratory Tract Infection (ARTI) and to study its association with day of illness on presentation and leucocyte count and severity of infection.

Materials and Methods: This is the cross-sectional study conducted on Paediatric patients of ARTIs coming to Krishna Hospital and Research Centre Karad. Patients of either sex between the age group of one to five years were selected. Immediately after the diagnosis of ARTI, blood sample was taken to investigate CRP levels and total leucocyte count. Age and weight of the patients, day of illness, symptoms and signs were also noted.

Results: Total 298 patients were included in the study. Fever, cough, rhinitis, throat pain, earache and breathlessness were the presenting symptoms. Out of these cough, fever and rhinitis were the most common symptoms of presentation. The percentage of positive CRP values was 14.4% i.e., in 43 patients this test was positive. In seven CRP positive patients leucocytosis was seen. Association of breathlessness with CRP positivity was observed.

Conclusion: Breathlessness which is one of the sign of severe respiratory tract infection and respiratory distress was present in most of the CRP positive patients. Leucocytosis was not associated with raised CRP levels. Thus, raised CRP values can be associated with severity of respiratory tract infection but cannot be taken as the sign of bacterial infection and may not be considered as an indicator for antimicrobial prescription.

Keywords: Breathlessness, Cough, Infection, Rhinitis

INTRODUCTION

CRP is an acute phase protein synthesised in liver. It was first described by Tillet and Francies Jr in 1930. They described it as serum factor responsible for precipitation of acute phase sera with C-substance of pneumococcal cell wall. It is so named because of C-polysaccharide of *Streptococcus pneumoniae* CRP is 120,000 to 140,000 molecular weight pentameric protein comprising of five identical monocovalently bound subunits arranged in cyclic symmetry on single plane [1,2]. CRP is having two major biological roles. It is known to activate the complement system and able to modify function of phagocytic leucocytes [3,4]. These effects support the concept that this serum protein may have a potentially central role in host defense mechanisms. Its production is mainly by Interleukin 6, Interleukin 1β and tumour necrosis factor in response to infection or tissue inflammation [5]. CRP, which is raised in different disease activities and inflammation, can be used as a diagnostic tool [6]. However, its role in differentiating bacterial infections from viral infection is not proved [7].

It is observed that synthesis of CRP starts within hours after a tissue injury or an infection. This indicates its probable role in innate immune response that contributes to host defense [8].

CRP binds with polysaccharides present on cell membrane of many microbes. Binding of CRP activates the classical complement pathway and opsonises (prepares) ligands for phagocytosis. It also neutralises the pro-inflammatory platelet activating factor and down regulates polymorphs [9]. Though, CRP levels are raised as a result of tissue injury or inflammation, it is not specific for any particular disease. However, its measurement helps us to diagnose and monitor the disease progression as well as therapeutic response.

The CRP molecules bind complement and enhance phagocytosis. The release of inflammatory mediators from activated mononuclear phagocyte cells constitutes an important part of the host response to infection. Of these mediators, Interleukin-6 is a major inducer of acute phase

proteins, including the CRP. Combining clinical parameters with CRP values may help us to decide whether the patient will get benefited from the treatment with antibiotics.

There is a correlation between onset of infection and levels of CRP. It is acute phase protein and values are reliable within first 24-48 hours [10]. CRP synthesis starts increasing within 4 to 6 hours after onset of inflammation or tissue injury. It may get doubled every 8 hours thereafter, and reaches its peak approximately at 36 to 50 hours [11]. In some studies investigators estimated CRP levels serially in patients with pneumonia who were on ventilator. They found if CRP levels are raised even after four days there was poor outcome in those patients. [12-13]. After treatment of inflammation or removal of inflammation this CRP concentration falls rapidly within 5-7 hours. Because of this reason present study was conducted to estimate the CRP values according to day of illness of patients.

MATERIALS AND METHODS

This cross-sectional study was conducted in Krishna Hospital and Research Center, Karad, Maharashtra, a tertiary health care center. Data were collected in the period of August 2014 to August 2017.

Inclusion criteria: Patients of age group between 1 to 5 years of either sex, suffering from acute respiratory tract infections, who presented to outpatient clinic and not taken any antimicrobial drug for at least last seven days for any reason.

Exclusion criteria: Patients with chronic liver disease, autoimmune disease, other systemic disorders and inflammatory diseases were not included in the study. All the patients included in our study had no history of any surgeries.

Approval was obtained from Institutional Ethics committee of the university. According to inclusion and exclusion criteria, patients were selected. Informed consent of parents/ guardians was obtained.

The patient who came to the outpatient clinic of the hospital was first examined by consulting pediatrician. After the patient was diagnosed with ARTI, drugs were prescribed. Informed consent from the parent/guardian was obtained, after which he/she was included in the study.

Blood samples were collected in plain vacutainer tube and then transported to Microbiology Laboratory for CRP testing and to Pathology Laboratory for leucocyte count. The serum samples were tested for CRP using slide test 'CRP' by semi quantitative method. Reagent used was 'RHELAX-CRP'. Testing was based on the principle of agglutination.

STATISTICAL ANALYSIS

Data was summarised into numbers, percentages, mean and standard deviation. Association of gender and CRP (presence/absence) with demographic variables, as well as symptoms was assessed by applying Chi-square test. Equality of age and weight of male and female patients was assessed by applying unpaired 't' test.

RESULTS

Total 298 patients of ARTI between age group 1 to 5 years were evaluated. Out of these, 190 were male and 108 were female children. The difference between the number of male and female children was not statistically significant. Maximum patients presented between 11-20 months of age which was 25.2%. It was found to be decreased gradually with increase in age. While the number was again found to be increased between age group 51-60 months and it was 22.1%. Mean weight of male children was 12.1 Kg. with standard deviation 3.4 and mean weight of female children was 11.5 Kg with standard deviation 3.2. Thus, mean weight of both male and female children was statistically similar.

We estimated CRP values in all 298 patients. Out of 298 in 43 (14.4%) patients CRP values were raised [Table/Fig-1]. Amongst these 32 were male children and 11 were female children. Though number of CRP positive male children was more than female children, difference is not statistically significant.

CRP values in CRP positive patients range from 0.6-18.8 mg/dL [Table/Fig-2].

The day of illness on presentation of these patients were also noted [Table/Fig-3].

Out of 43 CRP positive patients, 2 came on first day, 22 came on second and 19 patients came on third day of illness. Mean values of CRP were 9.7, 1.78 and 1.37 on first, second and third day respectively.

Presenting symptoms of patients were cough, rhinitis, fever, breathlessness, earache and throat pain. Cough was the common presenting symptom in maximum i.e., 286 (96%) patients. Next common symptoms noted were fever in 277 (93%) and rhinitis in 254 (85.2%) patients. Pain in the throat (sore throat) was observed in 31 (10.4%) patients and breathlessness was in 19 patients (6.4%). Earache was least

CRP	Positive	Negative	Total
Male	32	158	190
Female	11	97	108
Total	43	255	298

[Table/Fig-1]: Number of male and female patients with CRP positive values.

CRP values	Minimum	Maximum	Mean	Median	Mode	SD
Male	0.6	6.80	1.70	1.20	1.20	1.54
Female	0.60	18.80	2.80	1.20	1.20	5.35
Total	0.6	18.80	1.98	1.20	1.20	2.96

[Table/Fig-2]: CRP values (mg/dL) in male and female patients.

common symptom observed in our study which was found in only 6 (2%) patients [Table/Fig-4]. Number of the patients presented with three symptoms was 205 (68.8%). Number of patients presented with four symptoms was 37 (12.4%). Out of 242 cases presented with three (205) or four (37) symptoms, 224 were having cough, fever and rhinitis.

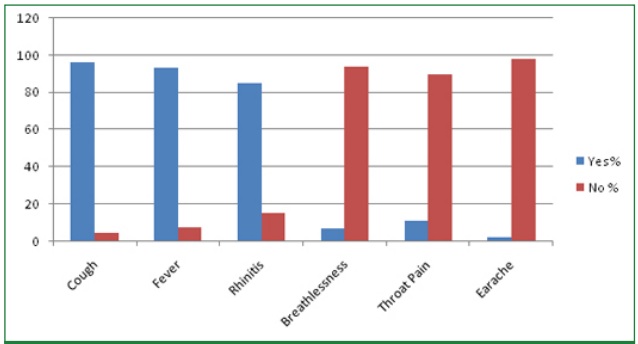
We have also analysed presence of different symptoms in CRP positive patients. And its statastical significance was analysed on the basis of p-values [Table/Fig-5]. With reference to presenting symptoms, association of cough, fever, rhinitis, earache, throat pain is not proved. But the association of breathlessness with CRP positvity was seen in our study (p<0.001).

Along with CRP levels, we calculated leucocyte (WBC) count of all patients. Normal leucocyte count ranges from 6000 – 15000/mm^3. Less than 6000/mm^3 (leucopenia) and more than 15000/mm^3 (leucocytosis) considered as pathological. Out of 298 patients, 224 were with normal range i.e. 6000 -15000/mm^3. Total 47 patients were having count less than 6000/mm^3 and 27 patients were having leucocyte count more than 15000/mm^3. We compared these WBC counts with raised CRP levels [Table/Fig-6].

Out of 43 patients with raised CRP values, 30 patients were having leucocyte count within normal limit. Six patients were having leucopenia and seven patients were having leucocytosis.

Day of Illness on Presentation	Total no. of Patients	No of Patients with Raised CRP Levels	CRP Range	Mean CRP
First	8 (2.7%)	2	0.6-18.8 mg/dL	9.7 mg/dL
Second	186 (62.4%)	22	0.6-4.8 mg/dL	1.72 mg/dL
Third	103 (34.6%)	19	0.6-6.8 mg/dL	1.38 mg/dL
Fourth	1 (0.3%)	-	CRP not raised	
Total	298 (100%)	43		

[Table/Fig-3]: Day of illness and CRP levels.



[Table/Fig-4]: Percentage of patients presented with different symptoms.

Symptoms		CRP +ve (n=43)	CRP -ve (n=255)	Chi-Square	p-value
Fever	Yes	42	235	1.71	0.191
	No	1	20		
Cough	Yes	43	243	2.1	0.146
	No	0	12		
Rhinitis	Yes	35	219	0.589	0.443
	No	8	36		
Throat pain	Yes	4	27	0.065	0.798
	No	39	228		
Earache	Yes	1	5	0.025	0.875
	No	42	250		
Breathlessness	Yes	8	11	12.589	<0.001
	No	35	244		

[Table/Fig-5]: Different symptoms in CRP positive patients.

Leucocyte Counts WBC/mm^3	CRP Positive	CRP Negative
< 6000	6	41
6000-15000	30	194
>15000	7	20
Total	43	255

[Table/Fig-6]: Correlation between leucocyte count and CRP positive patients.

DISCUSSION

We wanted to explore the association of raised CRP levels with day of illness, severity of disease condition, leucocyte count and nature of the infection i.e., whether it is bacterial or non bacterial. In our study, we tried to find whether to start antimicrobials for a patient based on CRP levels, so as to prevent further complications of the disease or avoid irrational over use of antimicrobials.

According to exclusion and inclusion criteria, 298 patients of ARTI were involved in the study. Though, there was higher number of male children as compared to female children it is not statistically significant. There is no statistical difference in the mean weight of male and female children.

Out of the total number of patients in the study, the maximum number of patients was from age group 11-20 months i.e., 25.2%. This suggests that respiratory tract infections are more common in this age groups. It is least common between 31-40 months (13.8%). But this percentage is again increased after 51 months i.e., after four years of age and it is 22.1%. This may be due to increased exposure to public places or contact with other children in pre school group.

Maximum number of patients i.e., 62.4% are brought to OPD on second day of illness and the number of male and female children out of their total number was almost similar i.e., 60.5%

and 65.7% respectively. This means parents immediately seek for medical help for their child and there is no gender disparity for seeking medical help. This study is conducted in rural area, but we observed that even in this area parents do not neglect the health of the child whether child is male or female, although it is reported that mortality due to pneumonia is higher in girls than in boys in India [14].

Common symptoms of presentation found in our study are cough (96%), fever (93%) and rhinitis (85.2%). Other symptoms observed were throat pain (sore throat), breathlessness and earache. Most of the patients presented with three or four symptoms from above. In 205 patients out of 298, cough, cold and fever were common symptoms observed. This observation coincides with the observation of Cotton M et al., [15]. In their study, cough and rhinitis were the most common symptoms of presentation and fever is seen only on day one of the illness. According to our study most of the ARTIs present with the symptoms of cough, rhinitis and fever. In study of Javadi A et al., they included pediatric as well as adult population. In adults along with coryza and cough, headache and musculoskeletal pain are commonly observed symptoms. While in pediatric patients along with coryza and dry cough, fever was associated symptom. They explained the reason for this was rhinovirus was the most common cause of ARTI in less than five years children, so fever was common symptom in them [16]. Our findings coincide with their findings.

We tried to correlate day of illness with CRP values, it was noticed that mean CRP levels were high in patients who presented on day one of the illness and this gradually decreased in patients presenting on second and third day. Melbey H et al., in their study measured CRP levels successively for seven days in ARTI patients and observed that CRP values decreases gradually with peak on 2-4 days without taking any antibiotic.

In our study CRP values were estimated in all these patients. The percentage of positive CRP values was 14.4% i.e., in 43 patients this test is positive/CRP values were raised. Though cough, rhinitis and fever were common symptoms of presentation, breathlessness was observed significantly in CRP positive patients ($p<0.001$) [Table/Fig-5]. Breathlessness was one of the sign of severe respiratory tract infection and respiratory distress. From this observation we can say breathlessness denotes severity of infection, which is seen in majority of CRP positive patients. Thus, positive CRP values are associated with severity of illness [17]. Leucocytosis is one of the sign of bacterial infection [18]. Some studies suggest that only raised CRP level is not indicative for bacterial infection [19]. In our study out of 43 CRP positive patients, in only 7 patients leucocytosis was seen and in majority of patients leucocyte count was within normal limit [Table/Fig-6]. That means raised CRP level is not indicator of bacterial infection. According to study by Melbye H et al., moderately raised CRP levels seen commonly in viral upper respiratory tract infection thus our findings coincides with their study [20].

LIMITATION

Limitations of our study are because of ethical issues we could not compare CRP values of children with ARTI with healthy children. We measured CRP values only on day of presentation and not serially on successive days.

CONCLUSION

Cough, rhinitis and fever were the most common symptoms of presentation. Mean CRP levels more in patients presented on first day and decreased gradually in patients presented on second and third day without receiving antimicrobials. Leucocytosis could not be correlated with raised CRP levels. We can conclude raised CRP levels will not be an indicator for starting antimicrobial drug therapy.

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