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RESEARCH ARTICLE

A PROSPECTIVE STUDY TO DETERMINE THE ROLE OF CRP DURING FEBRILE NEUTROPENIA IN PEDIATRIC MALIGNANCY

***Debasree Guha**

West Bengal Medical Council, India

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ABSTRACT

Febrile Neutropenia is a common and dreaded complication in children treated for malignancy. Current multi modality aggressive treatment of malignancy affects body's immune system in various pathways and renders the patient susceptible to infection by various infectious agents. Apart from infection there are other causes of fever in patients with malignancy (tumor itself, drug and blood product related). But detection of bacterial infection in febrile episode and early institution of antibiotic therapy is of paramount importance for overall survival of the patient. For this it is needed to choose good marker to detect infection. C-Reactive Protein is a cheap and widely available inflammatory marker is under investigation in this study to detect infection and monitor antibiotic therapy.

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INTRODUCTION

Febrile Neutropenia is a common complication in children treated for malignancy. Common pediatric malignancy include Acute lymphocytic leukemia (ALL) Hodgkin'sLymphoma (HL), Non-Hodgkin's lymphoma (NHL), Neuroblastoma. Although multimodality approach of therapy in malignancy have led to impressive improvement in cure rate for many pediatric malignancies, it has secondary effects on a variety of normal cells including skin, hair, mucous membrane and hematopoietic elements of bone marrow. Effects on hematopoietic cell led to bone-marrow suppression causing intermittent periods of leucopenia, thrombocytopenia and anemia of varying severity and duration. Fever is the principle sign of infection in neutropenic patient and frequently may be theonly evidence of infection. But apart from infection there are other various causes of feverin neutropenic patient with malignancy. These are- Fever associated with tumor itself, use of drugs in malignancy, associated with use of blood products. Feverin pediatric oncology patient is defined as Single oral or equivalent temperature of greater than 38.3°C (101°F) or two consecutive temperature greater than 38.0°C (100°F) in a 12 hour period lasting at least 1 hour[1]

****Corresponding author: Debasree Guha,***
West Bengal Medical Council, India.

Neutropeniais defined as an Absolute Neutrophil Count (ANC) < 500/ mm³ or < 1000/mm³ with an expected decline. Early identification of infection is still a challenge for clinicians. The general consensus is not to provide antibiotics for every suspected infection because of emerging issues with bacterial resistance. Therefore, a marker specific for bacterial infection will be most helpful. The body of literature concerning studies of the application of different inflammatory markers measurements in the pediatric and adult populations continue to grow. In our study our objective was to determine the role of C-reactive protein (CRP) in diagnosis of infection and monitoring of antibiotic therapy in febrile neutropenia in patients with pediatric malignancy.

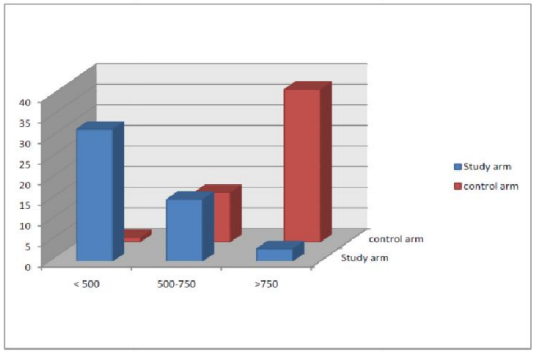
MATERIALS AND METHODS

This prospective study was conducted in department of Pediatric Medicine and Department of Oncology of a tertiary care hospital of Kolkata, India during the period of 2010-2012. Informed consent from patient and ethical clearance was taken. Age group of this study population was 1-18 years. Total study population was divided into two groups, Group A included 50 episodes of fever with neutropenia from 31 number of patients as cases and Group B included 34 patients having no fever with or without neutropenia in 50 episodes in different stages of treatment were selected as controls. Patients having liver dysfunction were excluded from our study.

In all episodes defined either as cases or controls detailed history was taken on predesigned and pretested proforma. The careful clinical examination was done to find any localized and generalized signs of infection and recorded accordingly. Complete blood count, CRP level were done in both groups before and after 7 days of antibiotic therapy in addition to pre therapy blood culture and liver function test(to exclude liver dysfunction). All data were collected, complied and were subjected to suitable statistical analysis by using appropriate statistical method. The computer software SPSS version 17, Microsoft office Excel 2007 were used for statistical analysis. Here simple statistical tools like Mean, Median, Mode, and Standard Deviation were used for calculation. Pearson's correlation Coefficient and Regression coefficient are used to establish correlation between the parameters. Qualitative parameters were analyzed by Chi-square test, Mann Whithey tests, Student T test. A p-value less than 0.05 was considered significant.

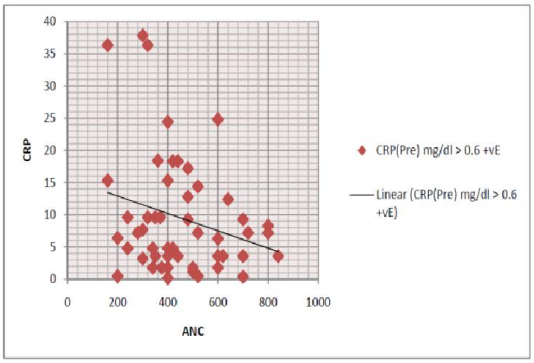
RESULTS

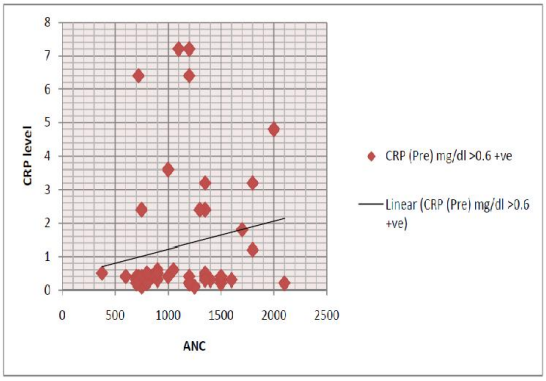
Mean age for Group A is 7.48 years and that of the Group B is 8.91 years with most of the patients are under 12 years in both groups. In Group A there is almost no difference in male, female distribution of patients, where as in control group slightly male prevalence is noted with male population constituted 58.82% of total population. In terms of distribution of patients according to the type of malignancy has shown most of the cases and controls are of ALL which comprised 58% in Group A and 50% in Group B, the next common type of malignancy in both groups were Biphenotypic Leukaemia and Non-Hodgkin lymphoma, both of them occupied 12.9% in total Group A population and 14.7% in Group B population. 64% of study population and only 2% of control population presented with severe neutropenia with ANC < 500/mm^3 before antibiotic therapy and it has shown a statistically significant difference with p value<0.0001. Post antibiotic therapy Absolute Neutrophil Count (ANC) of both Group A& Group B showed no statistical difference in Absolute Neutrophil Count after antibiotic therapy with a p-value of 0.0873, implying that both group responded well to antibiotic therapy.



Mean CRP level is high (9.51mg/dl) among case population, in control population it was 1.14 mg/dl with significant p value<0.0001. Post antibiotic therapy mean CRP level has also shown a significant difference between two groups p-value of 0.0036. Intra group pre & post therapy mean CRP level in both groups has shown statistically significant p value. Inter-correlation between pre-therapy ANC and CRP level in Group A population has shown a negative correlation (r= - 0.254.) and in that in Group B has shown a weakly positive correlation (r=0.172).

Post-therapy CRP level in relation to ANC in Group A & B respectively, have shown no correlation between these two Parameters with r= 0.048 and r= 0.089 respectively.





Analysis of blood culture positivity results has shown 36% of study population and 24% of control population had blood culture positivity, but most of the organisms isolated from Group B population was Coagulase negative Staphylococcus and that for the Group A shown pathogenic gram negative enteric organisms (E.coli & klebsiella) and among the 36% of culture positive patients in Group A 28% had severe neutropenia (ANC <500) and Positive CRP and most of the culture positive Group B (12% 0f total 24%) had moderate neutropenia and negative CRP.

DISCUSSION

Febrile Neutropenia is dreaded complication in pediatric malignancy. Detection of infection in patients with febrile neutropenia is of paramount importance though it is a really challenging one. The disease process itself or the current aggressive multimodality therapy including systemic antineoplastic and radiation therapy affect the body's immune system (Innate/ Acquired) in various mechanism renders the body susceptible to infection to various infectious agents (Bacteria, virus, fungus). Secondary effects of disease process itself or anticancer therapy to the hematopoietic elements of the bone marrow leading to depression of body's immune system. The differential diagnosis between neoplastic fever and infection in cancer patients has fascinated investigators for decades. The infection problems encountered in patients with solid tumors differ from those of neutropenic patients (e. g. AcuteLeukaemia). The complex series of reactions initiated in response to infection, physical trauma, malignancy is called the acute-phase response (APR). APPs have been defined as any protein whose plasma concentrations increases (positive acute-phase proteins; fibrinogen, serum amyloid A, albumin, C-reactive protein) or decreases (negative acute-phase proteins; albumin, transferrin, insulin growth factor I) by at

least 25 percent during anti-inflammatory disorder. Various studies were conducted on those inflammatory markers to denote infection in patients with febrile neutropenia. The C-reactive protein is one of the most studied inflammatory marker in this respect. In our study we had evaluated 50 episodes of febrile neutropenia from 31 patients with pediatric malignancy from 1-18 years of age. We had also selected 50 cases of pediatric malignancies without fever but with or without neutropenia as control from 34 patients. Commonest malignancy encountered in our study was Acute Lymphocytic Leukaemia (ALL), contributing about 58.06% cases (18/31 cases of Group A) & 50% of control population (17/34 cases of Group B) . This is consistent with majority of previous studies by *K P Schofield et al.* (1982)*, ATK Rau et al.* (2009)**,** *Grützmeier et al.* (1986). In contrast study by *Pedro Povoa et al.* (2011) showed Hodgkin's lymphoma as most frequent haematological malignancy in their study. Bi-phenotypic leukaemia (BL) & Non-Hodgkin's lymphoma (NHL) are next in place, each contribute 4 cases (12.9 % each) in study group. In control group next place there are Biphenotypic Leukaemia& Non-Hodgkin's lymphoma (NHL) contributing 14.76%. Though incidence of Hodgkin's lymphoma is more than that of Non-Hodgkin's type in this age group but in our study NHL has contributed more cases than HL probably due to small study group.In contrast study by *Pedro Povoa et al.* (2011) showed Hodgkin's lymphomaas most frequent haematological malignancy in their study. In ourstudyMean pre-therapy CRP level in febrile group (Group A) is 9.51mg/dl and that of the control group is 1.14 with a p-value < 0.0001 .This finding was almost consistent with previous study by *Vahap et al.* (2003) in which serum CRP the level of non-febrile period, 0.89 mg / dL, while the febrile period, 9:57 mg / dL with significant statistical difference 79(p = 0.0001). Femous*K P Schofield et al.* (1982) observed a serum CRP diagnostic value > 100 mg/ dl in 29 episodes of febrile neutropenic episodes from 22 patients they studied. Pre-therapy CRP positivity in relation to pre-therapy ANC in Group A shows a negativecorrelation with a correlation coefficient r= - 0.254 (Value less than 0) that implies that CRP level is high in patients with more severe neutropenia than patients with mild to moderate neutropenia. But in control group shows a weak positive correlation with a correlation coefficient r= 0.172 that means in this group CRP level is higher in patients with higher neutrophil count and in contrast to Group A all of the CRP positive episodes (26 %) have a ANC more than 500 / mm³. This type of correlation in control group is probably due to small sample size and 54% of total control population presented with actual neutropenia. Study by *Pedro Povoa et al* (2011) showed CRP concentrations were not influenced by theseverity of neutropenia (< 100/mm3 vs. _ 100/mm3 neutrophils), 25.1 ± 11.6 mg/dL vs. 26.9 ± 10.9 mg/dL, respectively (*P* = 0.527).

Blood culture positivity in our study shows no statistically significant difference between study and control group with p value= 0.99. In Group A only 36% and Group B 24% cases are blood culture positive for organism. This finding is compatible with study by *ATK Rau et al.* (2009) who demonstrated 38% of culture positive documented infection in their study among febrile patients, Study by *HannuSyrjala et al.* (2010) had shown 47.7% positive blood culture episodes in 327 leukemia patients. *Chinou et al.* (2005) found The pathogens were isolated from 64 blood cultures in 21 patients (25%) among 586 blood culture examined.b Organism isolated from Group A patients are Gram negative enteric organisms including E.coli, Klesiella. The vast majority of isolates from blood culture of control group were coagulase-negative staphylococci which are classified as nonpathogenic group of organism. In our study the Null Hypothesis was that "CRP is not helpful to detect infection in febrileneutropenia in pediatric malignancy". But here we were not able to establish this Null Hypothesis. In our study we have seen that febrile patients with neutropenia have higher and statistically significant level of CRP than afebrile patients with or without neutropenia at the start of antibiotic therapy. And CRP level become significantly lower in febrile group after a definite period (7 days) of antibiotic therapy consistent with elevation of ANC value. Mean CRP level is also high in febrile patients with blood culture positive for organisms.

Conclusion

So, in conclusion CRP is helpful to detect infection in malignancy patients during episode of febrile neutropenia and also helps in monitoring of antibiotic therapy in these patients as a cheap and widely available tool.

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