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CRP AND PROCALCITONIN LEVELS AS A PROGNOSTIC MARKER IN CHILDHOOD PNEUMONIA

Biochemistry

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ABSTRACT

Introduction :-Nowadays, PCT & CRP are known as a smart biomarker for sepsis and infection since it satisfies all the required criteria, that is, it has a high specificity and sensitivity, it is readily measurable, it is affordable and available in many hospitals, it is responsive and reproducible having half-life of 24 hours, it can be measured in a timely fashion. **Methodology:-** This study was conducted in Department of Biochemistry, Prasad Institute of Medical Sciences, Lucknow. The duration of study was over a period of two year. **Result:-**The result of this study revealed that Among the study group there were only 22 children in whom data for both CRP levels and PCT levels were available on the day one of inclusion in the study , the median levels of CRP & PCT were 12.8 mg/dl & 3.6 ng/ml respectively in children with SCAP on day one of study in whom both samples of CRP & PCT were available. **Conclusion:-**This study concludes that CRP and procalcitonin levels used as a prognostic marker in childhood pneumonia.

KEYWORDS

CRP , Procalcitonin, pneumonia

INTRODUCTION

Pneumonia is an important cause of morbidity and mortality in children worldwide with an estimated 146-159 million new episodes/year in developing countries, with approximately around 4 million deaths in children worldwide.[1-3] In developing countries it has a very high incidence rate and is responsible for 3 million deaths in children every year.[4]Pneumonia is responsible for 19% of all deaths in children below 5 years of age and 8.2% of disability and premature mortality as measured by disability adjusted life years (DALY).[5]

About 80% of all patients with community acquired pneumonia (CAP) are treated in an ambulatory setting, most of them without any diagnostic testing; this makes it harder to know the true etiology of pneumonia affecting these patients.[6]

C - reactive protein is an acute phase-protein synthesized only by the liver largely under transcriptional control of IL-6, [7] CRP levels rise rapidly in response to several inflammatory stimuli, bacterial infection being one of the most potent. The secretion of CRP begins within 4–6 hours of the stimulus, doubling every 8 hours, and peaking at 36–50 hours. After the disappearance of or removal of the stimulus, the CRP concentration decreases rapidly with a half-life of 19 hours.[8]CRP, even though being nonspecific, has proved to be helpful in establishing the etiology of some infections. A high CRP value (>100 mg/L) can indicate a severe bacterial infection.[9]

Procalcitonin is an inflammatory marker which has been shown to identify bacterial infection and predicting adverse outcome in hospitalized patients with critical illness.[10]

Role of CRP and PCT in predicting survival in ventilator-associated pneumonia concluded that measurement of PCT and CRP at onset and on the fourth day of treatment can predict survival of VAP patients and decrease in either one of these marker values predicts survival.[11] In a systematic review published in BMJ in 2005, it was stated that testing for C reactive protein is neither sufficiently sensitive to rule out nor sufficiently specific to rule in an infiltrate on chest radiograph and bacterial etiology of lower respiratory tract infection.[12] However, the advantage of CRP is that CRP levels can be used for the follow-up of pneumonia as well as to evaluate patient management and response to antibiotic therapy.[13]

The aim of this study is evaluation of CRP and Procalcitonin levels as a prognostic marker in childhood pneumonia.

MATERIAL & METHOD

Study Area:- This study was conducted in Department of Biochemistry, Prasad Institute of Medical Sciences, Lucknow.

Study Period:- The duration of study was over a period of two year.

Data Collection:- This was a prospective study in which children in age group of 1 month to 12 years were recruited. The written informed consent was obtained from either of parents of all the subjects undergoing the study. Daily clinical assessment and examination was done of all patients recruited in the study. Following investigations and follow up examinations findings were recorded:

- Hemogram, Total leukocyte count, Differential leukocyte count was done by Coulter and Band cells by microscopic examination.
- Tracheal aspirate / blind bronchial sampling (where ever possible).
- Acute phase reactants estimation on day 1 , day 3 & day 7 of inclusion in the study.

Data Analysis:-Data were analyzed by using Microsoft Excel.

RESULT:-

A total of 82 children were admitted with pneumonia in PICU during the study period of which, 57 children were diagnosed with severe pneumonia. Among the study group 32 (56.14%) were male children and 25 (43.86%) were female with male: female ratio of 1.28:1. The age distribution of the subjects is summarized in table 1: The presenting complaints of children in Severe community acquried Pneumonia (SCAP) and Nosocomial Pneumonia (NP) which includes both HAP & VAP children is summarised in Table 2. Among children with SCAP , the common presenting complaints were fever (92.3%), respiratory distress (89.7%) and cough (71.7%). Similarly in children with NP, respiratory distress (61.1%) & fever (55.6%) were the most common presenting complaints. Fever and respiratory distress were significantly more common in SCAP than in NP (p value < 0.05) .Loose stools and chest pain were seen in SCAP group only. The proportion of children who had anemia in SCAP (31,84.6%) was almost equal to those in NP (17,88.9%), however no significant difference was seen between the two groups ($p > 0.05$). Children with abnormal leukocyte count were proportionally higher in NP (11,61.1%) than in SCAP (17, 34.5%),however no significant association was seen on analysis between the two groups ($p > 0.05$).In our present study, there was no significant difference in children who had hyponatremia in SCAP (20, 51.2%) and NP (12, 55.6%) ($p > 0.05$). On Arterial blood gas analysis of children in our present study on inclusion ,there was significant association seen in the SCAP and NP group in children who were suffering from Respiratory acidosis & Metabolic Alkalosis ($p < 0.05$). Both respiratory Acidosis & Metabolic Alkalosis was common in NP than SCAP,however the no. of patients was less in both the groups.

Serial C -reactive protein (CRP) level and Procalcitonin (PCT) levels were assessed in children who were included in the study group on day one ,day three & day seven of inclusion in study. CRP levels were analysed in 38 children of SCAP (97.5%) on day one of study .Similarly PCT levels were possible in 14 children with SCAP (36%) . Median levels of CRP and PCT in these children were 12.8 mg/dl and 3.6 ng/ml respectively.

Among the study group there were only 22 children in whom data for both CRP levels and PCT levels were available on the day one of inclusion in the study , the median levels of CRP & PCT were 12.8 mg/dl & 3.6 ng/ml respectively in children with SCAP on day one of study in whom both samples of CRP & PCT were available.The children with SCAP were divided into two groups based on their outcome data as those with Survival group (children survived) and mortality group (children died). Four children who left the hospital against medical advice were excluded from the categorization. Data on CRP levels and PCT levels from SCAP cases is summarized below.

When initial CRP levels were compared among the groups, data revealed that there was no significant difference in the CRP levels among the two groups at the time of inclusion of such children in the study. Moreover, there was no significant change in CRP levels as the ICU stay of these children increased in both groups irrespective of progression of disease.

Table 1-Age & Sex Distribution Of Children Included In The Study.

Age	Male	Female
1 mth -3 mth	4	4
3 mth-12 mth	14	12
1 yr-5 yr	8	7
5yr - 12 yr	5	2
Total	32	25

Table 2- Presenting Complaints Of Children Included In SCAP & NP.

	Presenting Complaints	SCAP (n=39)	NP (n=18)	P value
1.	Fever	36 (92.3%)	10 (55.6%)	< 0.05
2.	Respiratory Distress	35 (89.7%)	11 (61.1%)	< 0.05
3.	Cough	28 (71.7%)	9 (50%)	> 0.05
4.	Decrease acceptance of feed	7 (18%)	5 (27.8%)	> 0.05
5.	Loose stools	4 (10.3%)	0	> 0.05
6.	Seizures	3 (7.7%)	3 (16.7%)	> 0.05
7.	Lethargy	3 (7.7%)	2 (11.1%)	> 0.05
8.	Chest pain	1 (2.5%)	0	> 0.05

Table 3. Laboratoy Findings Of SCAP and NP.

	SCAP (n=39)	NP (n=18)	P value
Anemia[a]	31 (84.6%)	17 (88.9%)	> 0.05
Abnormal leukocyte count[b]	17 (43.5%)	11 (61.1%)	> 0.05
Hyponatremia[c]	20 (51.2%)	12 (55.6%)	> 0.05
Acid Base disturbance			
1. Metabolic acidosis	10 (25.6%)	4 (22.2%)	> 0.05
2. Metabolic alkalosis	0	2 (11.1%)	< 0.05
3. Respiratory Acidosis	0	1 (5.6%)	< 0.05
4. Respiratory Alkalosis	6 (15.4%)	1 (5.6%)	> 0.05
5. Mixed	4 (10.3%)	3 (16.7%)	> 0.05

a. Anaemia classifications were based on WHO proposed definitions.[122,123]
b. Lower values for leukocyte count for the 5th percentile and upper values for
leukocyte count for the 95th percentile.[120]
c.Hyponatremia was defined as serum Na level less than 135 meq/l.

Table 4-CRP Levels Comparison Among Mortality Group & Survived Group Of Children With SCAP.

	Mortality Mean ± SD	Survived Mean ± SD	P value
CRP Day 1 (mg/dl)	9.68 ± 5.06 (10)*	7.70 ± 5.70 (24)*	> 0.05
CRP Day 3 (mg/dl)	8.9 ± 5.43 (8)*	6.61 ± 5.60 (23)*	> 0.05
CRP Day 7 (mg/dl)	6.4 ±5.54 (3)*	4.27 ± 4.79 (18)*	> 0.05

* Number of patients in whom data was available and were anlaysed.

Table 5-PCT Levels Comparison Among Mortality & Survived Group Of Children In SCAP.

	Mortality Mean ± SD	Survived Mean ± SD	P value
PCT Day1 (ng/ml)	123.07 ±158.50 (4)*	8.45 ± 14.61 (8)*	< 0.005
PCT Day3 (ng/ml)	140.18 ±164.82 (4)*	5.43 ± 10.31 (12)*	< 0.005
PCT Day7 (ng/ml)	68.63 ± 93.24 (2)*	1.44 ± 1.62 (7)*	< 0.005

* Number of patients in whom data was available and were anlaysed.

DISCUSSION

Pneumonia is the leading cause of mortality and morbidity in children. Recent estimates from the World Health Organization (WHO) suggest that pneumonia is responsible for 20% deaths in children under five years of age, leading to 3 million deaths per year. Of these deaths two-third occur during infancy and more than 90% occur in the developing countries.[14-15]

In India recent estimates of under-five children suggest that 13% of deaths & 24% of national burden of disease is due to pneumonia.[16] Hospital based studies have reported that 20-30% of admissions in under-five year age group in children are due to pneumonia.[17] Various interventions were initiated to reduce pneumonia related mortality & morbidity.[14-18] In 1983, World Health Organization initiated the Acute Respiratory Infection control program which led to decline in Infant Mortality Rate by 10.7 (4.8-16.7) deaths per 1000 live births and under five mortality by 36 deaths per 1000 live births.[17]

In the present study, no significant difference was observed in proportion of males (56.14%) and females (43.9%) patients, signifying that severe pneumonia does not have any sex predisposition. Previous studies also confirmed the above fact,[18-20]. However Srinivasan et al on multivariate analysis, showed that female gender is associated with increased chances of developing VAP.[21]

Many studies have been conducted probing the utility of biomarkers like CRP and PCT in the diagnosis of severe pneumonia in children.[22-32] Few other studies have assessed the role of PCT in differentiating viral pneumonia from bacterial pneumonia in children.

In the present study there have been 39 cases of community acquired pneumonia. A total of twenty two patients of SCAP could be assessed for role of CRP and PCT in the diagnosis of severe pneumonia in children. Data reveals that there was no significant difference in the CRP levels of patients on day 1 of the inclusion in the study group (mean CRP levels of 9.7 mg/dl in mortality group of SCAP and 7.7 mg/dl in patients suffering from SCAP with survival group). As such the prognostic ability of CRP remains poor. This was in concurrence with the earlier published studies. [31-32] However, role of CRP in diagnosis of severe pneumonia cannot be totally negated in the current study due to limitation of method in assessment of CRP levels. The CRP levels were assessed using latex agglutination kit with semi-quantitative method. This leads to limitation in the upper levels being reporting in the current study to ≥ 12.8mg/dl. When calculating mean values for such patients the value of CRP was taken as 12.8mg/dl which may lead to falsely lowered mean/median values of CRP in patients with much higher CRP levels.

Median levels of PCT in the published studies have been found similar to those of children in the present study.[32] A study on PCT kinetics in prognosis of SCAP suggested median PCT levels as 5.2 ng/ml on day 1 and 2.9 ng/ml on day 3.[33] In yet another study on 126 children with bacterial pneumonia had PCT (median 2.09 ng/ml) and CRP concentrations (96 mg/dl).[64] In the present study median PCT levels were 3.9 ng/ml on day 1; 2.3 ng/ml on day 3, and 0.75 ng/ml on day 7. When assessed for SCAP cases only, median PCT levels were 10.5 ng/ml on day 1 and 1.0 ng/ml on day 3. Interestingly, there has been no study till date comparing mean PCT levels in cases of severe pneumonia among the survival to that of mortality. In present study when this data was analysed there was significant difference in the mean PCT levels among those who survived to those children with mortality. The levels were raised on day 1 which continuously fell on day 3 and day 7 in commensuration with survival. However, children with mortality had significantly higher PCT levels on day 1. Although, levels do fall in this group too, but absolute levels remains high (mean PCT levels of 140 on day 3 and 68 ng/ml on day 7) indicating that absolute PCT levels along with falling trend of PCT can be used to predict outcome of severe pneumonia cases in children.

CONCLUSION

This study concludes:
1. When initial CRP levels were compared among children with Mortality and Survivor group, there was no significant difference in the CRP levels among the two groups at the time of inclusion of such patients in the study. Moreover, there was no significant change in CRP levels as the ICU stay of these children increased in both groups irrespective of progression of disease.
2. PCT levels provide good insight to the disease pathology and

progression. There was significant difference in the initial levels of PCT among the children with mortality and survivor group (p value < 0.005). Children who were successfully discharged from PICU show gradual decrease in levels of PCT, however the levels of PCT in children with mortality also decreased but their levels were considerably higher those from children who survived.

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