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Original Article

Procalcitonin Level and Organ Dysfunction in Children with Sepsis: A Prospective Observational Study

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Abstract

Background
Procalcitonin is produced in response to endotoxin or mediators released in response to bacterial infections and are reported to be sensitive predictor of sepsis and multiple organ failure. The main aim of this study was to correlate procalcitonin levels with the severity of organ dysfunction in children with sepsis.

Materials and Methods
A prospective observational study was done among children aged >1 month - 18 years admitted for sepsis in level 4 pediatric intensive care unit at Rainbow children Hospital, Hyderabad from July 2018 to January 2020. Children with sepsis due to burns and trauma were excluded. Procalcitonin levels were assessed on days 1 and 5 and were analyzed using descriptive statistics. P value of < 0.05 was considered significant wherever applicable.

Results
Among 369 cases, procalcitonin levels showed positive correlation with severity of illness and multiorgan failure as evidenced by pediatric risk of mortality III score (mean score 6.44 ± 3.79) and worst sepsis-related organ failure assessment score (mean score 7.11 ± 4.27) respectively. Duration of non-invasive ventilation, invasive ventilation, pediatric intensive care unit stay, and mortality were significantly high in children with higher procalcitonin level. Mean procalcitonin level were significantly higher in culture positive cases (65.79 ± 77.10) compared to culture negative cases (37.99 ± 45.81).

Conclusion
In this study, positive correlation was observed between procalcitonin level and multiple organ dysfunctions in sepsis and septic shock.

Keywords: *Multiple organ failure, Procalcitonin, Sepsis*

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Introduction

Sepsis is the leading cause of multiorgan dysfunction syndrome (MODS) in children and the latter is the common associate of former (17-73%), particularly with severe sepsis [1-3]. Occurrence of MODS is associated with higher mortality and longer stay in intensive care unit (ICU). Sepsis-related organ failure assessment (SOFA) score is the gold standard for the diagnosis and assessing prognosis in these patients [3].

Procalcitonin (PCT) is reported to be sensitive predictor of sepsis and MODS [4] with sensitivity and specificity in diagnosing sepsis being 89% and 94% respectively [5]. Yet it is unclear whether PCT is predominantly influenced only by inflammation induced by microbial infections, or also by the severity of MODS secondary to the systemic inflammatory response. Recent investigations have mainly focused on sepsis-related severity scores and PCT level, but data on relation of PCT concentrations to MODS are scarce.

The main aim of this study was to correlate PCT levels with the severity of organ dysfunction in children with sepsis. The secondary objective of this study was to correlate PCT concentrations with outcome, different organ involvement, culture positivity, duration of ventilation and hospital stay in children with MODS with sepsis.

Materials and Methods

A prospective observational study was carried out in the department of Pediatrics, Rainbow children Hospital, Hyderabad over a period of 18 months from July 2018 to January 2020 after taking ethical approval from the Institutional Ethics Committee (EC approval no RCHBH/082/03-2018). Children aged >1 month - 18 years admitted in pediatric intensive care unit (PICU), who underwent PCT test for sepsis at the time of hospitalization and subsequently were included in the study. Children with sepsis due to burns and trauma were excluded. The convenience sampling technique was used and the sample size was calculated using the following formula, [$n = Z^2Pq/e^2$, $=1.96^2*0.5*0.5/0.06^2 = 267$] Where, n = minimum required sample size, Z = 1.96 at 95% Confidence Interval, p = prevalence is taken as 50% for maximum sample size calculation, q = 1-p, e = margin of error, 6%. Adding a 10% non-response rate, the calculated sample size was 294. However, a sample size of 369 septic patients was taken.

PCT is detectable within 2 to 4 hours after a triggering event and peaks by 12-24 hours. Its levels increase rapidly in children with sepsis, and are a better indicator of prognosis compared to C-reactive protein (CRP) [6]. PCT was estimated on days 1 and 5 of admission using chemiluminescent emission method, which is measured by photomultiplier. Severity of organ dysfunction was assessed Sequential organ failure assessment (SOFA) score is used as a predictor of outcome of sepsis in the pediatric intensive care unit. Severity of organ dysfunction was assessed by the SOFA score which is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems each scored from 0 to 4 with an increasing score reflecting worsening organ dysfunction. SOFA score and its change over time is used for assessment of morbidity in critically ill children. It is traditionally calculated on admission and at each 24 hour period following admission. Clinical profile including patients' demographics (age, gender, weight), primary underlying disease, disease severity scores (Pediatric Risk of Mortality (PRISM-3), SOFA score), serial PCT level from the time of hospitalization, time of initiation of Respiratory support or Mechanical Ventilation, oxygenation parameters (mainly Oxygen Index) and hemodynamic support was collected (Table 1). Based on PRISM III score in first 24 hours of admission, highest PCT level were studied. PRISM III score was divided into different groups to analyze severity of illness and level of PCT correlation. Similarly, to analyze relation between multiorgan failure and procalcitonin level, cases were divided into different subgroups based on worst SOFA score and relation were studied (Table 2).

Data were entered and analyzed in IBM SPSS Statistics 25.0. Obtained data were expressed in frequency, percentage, mean and standard deviation as applicable for qualitative data as descriptive statistics. 95 % confidence intervals were estimated. Comparison between numerical and categorical groups was done by Student's t-test and comparison between categorical data was analyzed by chi-square test and one way ANOVA test. P value <0.05 was considered as significant level.

Results

Out of 369 children included, 224 (60.70%) were male and 145 were female (39.29%). Mean age was 3.95 ± 4.14 years. Mean PRISM III score was 6.44 ± 3.79 and mean worst SOFA score was 7.11 ± 4.27. Mean duration of PICU stay was 6.14 ± 5.27 days. Mean PCT levels among discharged cases (n=302) was 40.38 ± 26.32, death cases (n=36) was 59.63 ± 38.82 and among cases which left against medical advice (LAMA) (n=31) was 54.69 ± 46.48.

Table 1: Baseline Demographic Features, Characteristics and Outcome.

Characteristics	Categories	Results	p value
Mean age at diagnosis (year)		4.95 ± 4.34 years	
Gender, n (%)	Male	224 (60.70%)	
	Female	145 (39.29%)	
PRISM III score (mean ± SD)	Not applicable	6.44 ± 3.79	
Mean worst SOFA score	Not applicable	7.11 ± 4.27	
Mean PCT level based on day of illness (ng/ml)	DAY 1	35.65 ± 44.37	
	DAY 3	44.50 ± 74.14	
	DAY 5	35.61 ± 62.42	
	DAY 7	35.71 ± 57.02	
	> 7 DAYS	27.05 ± 38.12	
Mean PCT level based on primary organ of involvement (ng/mL)	Highest PCT	45.80 ± 57.51	Spearman's rho of – 0.38
	Musculoskeletal	74.64 ± 38.52	
	Pulmonary	33.20 ± 19.81	
	Cardiovascular	54.58 ± 16.32	
	Central nervous system	32.50 ± 28.82	0.465*
	Gastrointestinal	40.13 ± 26.78	
	Tropical Infection	30.96 ± 18.89	
	Metabolic	1.61 ± 0.88	
	Renal	40.44 ± 26.67	
	Skin and soft tissue	23.78 ± 18.89	
Mean PCT level based on respiratory support requirement (ng/mL)	NIV (n=139)	45.32 ± 33.68	< 0.0001
	No Respiratory support (n=98)	26.81 ± 18.86	
	Mechanical Ventilation (n=132)	63.45 ± 46.42	<0.0001
	Non Ventilated (n=98)	26.81 ± 18.86	
Mean duration of PICU stay		6.14 ± 5.27 days	
Mean PCT level based on severity of illness	Sepsis (220 cases)	29.36 ± 11.48	<0.0001
	Septic shock (149 cases)	42.12 ± 18.32	
Outcome	Discharge (302 cases)	40.38 ± 26.32	0.0001
	Death (36 cases)	59.63 ± 38.82	
	LAMA (31 cases)	54.69 ± 46.48	

Table 2: Correlation of Procalcitonin level with PRISM III score and worst SOFA score

	PRISM III Score	n	Mean ± SD (Mean PCT level)	p-value
PRISM III	0-7	207	36.78 ± 54.71	
	8-15	114	47.76 ± 51.36	
	16-23	38	71.05 ± 67.03	0.001
	23-34	10	109.73 ± 76.31	
	Total	369	45.68 ± 57.48	
Worst SOFA score	0-5	165	29.62 ± 39.30	
	6-10	130	46.99 ± 47.78	
	11-15	56	81.69 ± 97.23	
	16-19	15	72.22 ± 36.49	
	20	3	66.87 ± 31.93	0.001
	Total	369	45.67 ± 57.48	

There was a statistically significant (p=0.001) positive correlation between PCT with increase in severity of illness as evidenced by PRISM III score (Table 1). PCT level progressively increased with increasing incidence of multiorgan failure, as shown by worst SOFA score (Table 2). There was positive correlation (r= 0.798, p=0.001) between worst SOFA and highest PCT was analyzed by Pearson's correlation (Figure 2). Similarly, there was a statistically significant (r=0.664, p=0.001) relation between SOFA on first day and PCT level on first day.

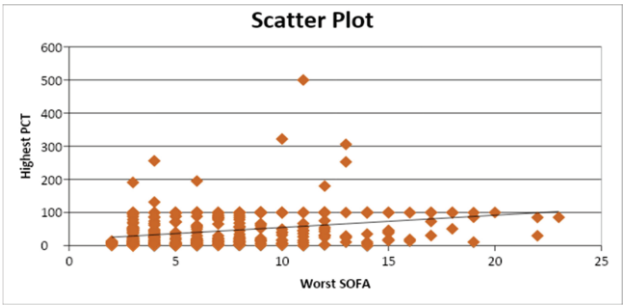

Figure 1: Positive correlation with highest PCT level with multiorgan failure.

Based on culture positivity, relation of highest PCT and culture positivity was studied (blood c/s, ET c/s). The mean PCT was 45.68± 57.48; there was a statistically significant difference (p=0.001) in mean PCT level between culture positive (n=102) (mean PCT 65.79 ± 77.10) and culture negatives (n=267) (mean PCT 37.99 ± 45.81).

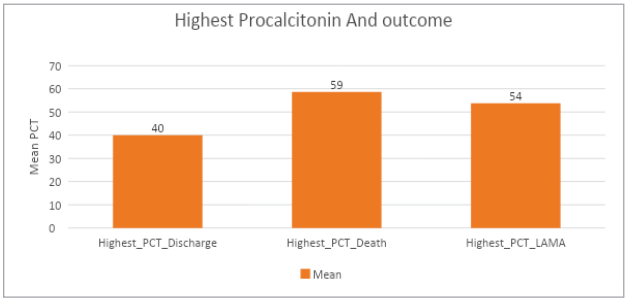

Figure 2: Highest Procalcitonin level with out come

Mean PCT level was higher in children who died or went on LAMA. One-way ANOVA with post hoc analysis showed this difference was statistically significant in group who survived and who had death.

Day 1 and day 5 PCT data was available for 121 children, of whom, 90 (74.4%) survived, 24 (19.8%) died and seven (5.8%) went on LAMA. PCT concentration decreased in 96 (79.34%) and increased in 25 (20.66%) but change in concentration was not associated with mortality (p=0.73). There was a statistically significant difference (p=0.001) between mortality and decrease in PCT concentration (< 50% Vs > 50% decrease, 31.6% Vs 10.8%). There was no significant correlation between increasing trend of PCT on Day 1 and Day 5 with mortality.

Discussion

Previous studies have documented the usefulness of PRISM III in MODS as a predictor of outcome and mortality. SOFA score can predict the short-term outcomes in sepsis [6]. Studies favor the use of PCT and SOFA score for assessing the severity of infection, to predict the prognosis, disease course and outcome [7]. Its utility in assessing the septic shock has been documented [8]. The mean PRISM III score in our study population was 6.44 ± 3.79 and mean worst SOFA score was 7.11 ± 4.27. Mean PCT was 45.80 ± 57.51 and the levels were low on days 1 and 2. Metabolic cause resulted in very low levels of PCT (1.61ng/dL ± 0.88), followed by skin and soft tissue infections (23.78 ± 18.89) and tropical infection (30.96 ± 18.89); Mean PCT levels were low in those without respiratory support (26.81 ± 18.86), sepsis (29.36 ± 11.48).

Our study showed a positive correlation of PCT level with higher PRISM III score, suggesting the severity of illness, similar to the observations by Casado-Flores et al [6] who studied 80 children with suspicion of sepsis and reported the better diagnostic and prognostic utility of PCT, and that levels were significantly more elevated among children with higher PRISM score. In our study, PCT level were progressively increasing with increasing incidence of multiorgan failure, as shown by Worst SOFA score similar to study done by Haasper et al [9] which showed an elevated PCT level preceding the development of MODS by 3 days [8]. There was no significant relation of PCT level with organ of involvement in our study, which was in contrast to study by Moulin F et al. where PCT was significantly increased in bacterial infection of respiratory tract.

Our study showed increased need of non-invasive, mechanical ventilation, ionotropic support and increased duration of PICU stay in child with higher PCT. In our study, those who were culture positives (65.79 ± 77.10) had higher PCT levels (culture negative, 37.99 ± 45.81) (p=0.001), which is similar to the observations of Mandell IM et al [10]. In our study, mean PCT level was higher in those who died or went on LAMA as compared to survivors (p <0.0001), similar to the observations of Meng et al [11]. Higher PCT level in children who went on LAMA could be attributed to poor prognosis being reason for LAMA in most of cases.

Admission PCT correlates with severity of infection, and its fall after 24 hours of initiating treatment is considered as good prognosis [12]. Trends of PCT level on day 1 and day 5 revealed favorable outcomes in children with day 5 PCT level in decreasing trend > 50% in our study. Persistently elevated PCT in children with bacterial infection or sepsis signifies poor outcome [13]. We could not elicit significant correlation between increasing trend of PCT on Day 1 and Day 5 with mortality, which could be attributed to escalation of antibiotics and supportive care following gradual rise in PCT level in our study. Studies have indicated that high procalcitonin level on serial monitoring on day 1 and day 5 correlates with severity of multi organ dysfunction syndrome in children [14]. We found that admission PCT level correlated positively with admission SOFA score, similar to the study by Hathril et al [12]. In addition, Hathril et al. also noted that children whose levels of PCT remained elevated were at much greater risk of severe disease and death than those whose levels dropped in response to therapy. In this study, highest PCT had strong, statistically significant (p<0.0001) positive correlation with worsening of multiorgan failure. High procalcitonin level at admission and continuous elevation on day 5 is reported to be an independent predictor of all-cause mortality.

This is a single-center, observational study with limited sample size. Only children with suspicion of sepsis whose PCT levels were measured were included. We studied only cases with sepsis and no controls were included in this study. Therefore, selection bias could not be ruled out. Our results need to be validated on prospective larger patient population.

Conclusion

In this study, there was positive correlation between PCT level and increasing severity of illness and organ dysfunction in children as indicated by PRISM III Score and Worst SOFA Score.

Recommendation

PCT level can predict worsening of organ dysfunction, need of prolonged PICU stay, need of invasive and noninvasive ventilation, and survival, if serially monitored. Decrease in PCT more than 50% during serial monitoring can predict favorable outcome in children with sepsis.

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Conflict of intrest: None

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