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ORIGINAL ARTICLE

Procalcitonin: A Useful Biomarker of Sepsis in Children

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ABSTRACT
This study was used to determine the diagnostic efficacy of Procalcitonin as biomarkerfor paediatric sepsis and to determine the use of Procalcitonin in prognosticating sepsis inchildren.
Keywords: Procalcitonin, Biomarker, Paediatric intensive care units (PICU)

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INTRODUCTION

Sepsis constitutes a major problem in paediatric population. Morbidity and mortality in Paediatric intensive care units (PICU) are commonly related to severe infections and sepsis [1]. Clinical data alone may be unreliable in distinguishing between patients with bacterial sepsis and non-bacterial systemic inflammatory response syndrome (SIRS) [2]. Sepsis is a heavy burden on health services all over the world, both from economic and social points of view. According to an epidemiological studyof the USA, over the last 20 years, the incidence of sepsis increased from 82.7 to 240.4/100 thousand inhabitants, as did the deaths related to it, although the general mortality rate among patients with sepsis was reducedover the period [3].

Sepsis is a complex syndrome caused by an uncontrolled systemic inflammatory response, of infectious origin, characterized by multiple manifestations and which can result in dysfunction or failure of one or more organs and even death. During sepsis, circulating phagocytes are activated and multiple mediators are released into blood. The balance between proinflammatory and anti-inflammatory responses affect the outcome of a sepsis patient. In predicting the outcome, the markers of systemic inflammation may help to identify patients at risk of severe sepsis or septic shock at an early stage of the disease. Not all patients who appear septic demonstrate an infection, and the widespread administration of antibiotics to all these patients carries problems ofantibiotic resistance, of drug toxicity, and of increased medical costs. Thereis a need for an effective and accurate biochemical marker to support, or exclude, the diagnosis of infection. The lack of specific early markers of infection may be responsible in part for withholding, delaying or unnecessary antimicrobial treatment in critically ill patients [6]. Thus, there is unmet need for laboratory tools that can distinguish between SIRS fromsepsis.

A sepsis marker should be useful for early diagnosis and characterized by high sensitivity and specificity. It should be related with the disease importance and have prognostic value. The available markers are numerous: white blood cell count (WBC), C - reactive protein (CRP), procalcitonin (PCT), endotoxin, cytokine, receptor for Interleukin 1(IL-1), complement factors, endotelin-1, phospholipase A2, prostaglandins (PGE 2), lactoferrin, neopterin and elastase. However, none of them are specific to sepsis and diagnosis must be evaluated in the context of the clinical evidence of sepsis. Various markers of sepsis including C- Reactive protein, tumour necrosis factor (TNF) α, Interleukin -1β (IL-1β), Interleukin-6 (IL-6) and Interleukin (IL-8) have all been studied for their ability to differentiate SIRS from sepsis [6-9].

PCT has been established in studies to be a more reliable marker in early neonatal sepsis than either CRP or IL-6 within the first 12 hours of life. Studies in adults have shown high accuracy in PCT levels [2]. Conflicting results exist about the role of PCT in children. There are paucity of studies in children that have assessed role of PCT in paediatric sepsis cases. Hence there is need to define the role of PCT in paediatric

sepsis. Hence we planned current study to determine the diagnostic efficacy of Procalcitoninas biomarker for paediatric sepsis.

MATERIAL AND METHODS

STUDY DESIGN: Cross sectional Study

STUDY POPULATION: The study population consists of all children aged 2 months to 14 years admitted with sepsis in the PICU in Sree Balaji Medical College andHospital.

STUDY PERIOD: One year from January 2019 to January 2020**.**

STUDY PLACE: The study was came out in the Department of Paediatrics at Sree BalajiMedical College and Hospital, Chennai.

SAMPLE SIZE: 50 children with sepsis will be included in this study.

INCLUSION CRITERIA:

1. Consecutive paediatric children aged 2 months to 14years admitted with sepsis and whose parents / guardian have given consent was beincluded in this study.

EXCLUSION CRITERIA:

1. The Children who have received antibiotic therapy
2. The Children with chronic systemic disease, primary and secondaryimmunodeficiency, inflammatory disease like autoimmune disease, Chronic Kidney Disease, Malignancies
3. Parents not willing to give consent to the study

ETHICAL COMMITTEE APPROVAL:

Ethical committee approval for this study was sought from the Institutional Human Ethics Committee of Sree Balaji Medical College andHospital, Chennai.

METHODS

The questionnaire containing the sociodemographic details of family was recorded. At admission, the weight and the vitals was be recorded in all patients. Written consent was be obtained from parents forthe use of blood samples. Definitions for sepsis in paediatrics was defined as per the International Paediatric Sepsis Consensus Conference Statement.

SIRS: Systemic inflammatory responses, ACCP: American College of Chest Physicians, SCCM: Society of critical care medicine, WBC: White blood cell count

The diagnosis of sepsis was made when patients have clinical findings of infection hyperthermia or hypothermia, tachycardia and tachypnoea, and positive blood culture. All children admitted were investigated as per the study protocol:

D1: At the time of admission – complete blood count, Procalcitonin, CRP,Blood culture and other culture as necessary based on the clinical presentation and organ system involvement.

D3 and D5 investigations may be repeated if necessary

On admission detailed history and clinical examination was done. Children were assigned the septic classification as SIRS, Sepsis, Septic shock and Severe Sepsis according to international consensus conference on admission. Since there is a possibility that a patient with sepsis will progress to septic shock, the initial diagnosis on admission was consideredthe definitive criterion for assigning study group. Investigations like complete blood counts, Blood culture, serum CRP and serum procalcitoninwas done for all the cases.

BLOOD SAMPLE COLLECTION

A consent form for blood collection was obtained from the parents.Well trained nurses followed standard methods to withdraw blood and care was taken to prevent the blood resulting in clot formation and hemolysis. Venous blood was collected under aseptic orders using a 5 ml disposable syringes. Then the sample was transferred into containers containing EDTA (ethylene diamine tetra- acetic acid) for complete blood count and CRP analysis. Then the sample was transferred under suitable conditions, to our central laboratory for further processing.

PCT Estimation

PCT was measured using an immunoluminometric assay in our study. The BRAHMS PCT LIA is an immunoluminometric assay (ILMA) that measures PCT levels in human serum and plasma. There are two antigen-specific monoclonal antibodies administered in excess that bind PCT (antigen) at two separate binding sites (calcitonin and katacalcin segments). One of these antibodies (the tracer) is luminescence tagged, while the other is attached to the tube's inner walls (coated tube system). Both antibodies react with PCT molecules in the sample during incubation to produce "sandwich complexes." As a result, the luminescence labelled antibody adheres to the tube's inner surface. The surplus tracer is taken from the tube and discarded once the reaction is complete.

The amount of leftover tracer on the test tube wall is then determined by utilising an appropriate luminometer and the BRAHMS Basiskit to measure the luminescence signal.

Statistical Methods

X was / were considered as primary outcome variable / variables. Ywas / were considered as Secondary outcome variable / variables. Z was considered as primary explanatory variable.

Descriptive analysis was carried out by mean and standard deviationfor quantitative variables, frequency, and proportion for categorical variables. Non normally distributed quantitative variables were summarized by median and interquartile range (IQR). Data was also represented using appropriate diagrams like bar diagram, pie diagram andbox plots.

The D1 PCT, D2 PCT, D3 PCT in predicting outcome was assessed by Receiver Operative curve (ROC) analysis. area under the ROC curve along with its 95% CI and p value are presented. Basing on the ROC analysis, it was decided to consider 101, 101, 93 as the cut off value. The sensitivity, specificity, predictive values and diagnostic accuracy of the screening test with the decided cut off values along with their 95% CI werepresented. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

RESULTS

A total of 50 subjects were included in the final analysis.

Table. 1 Distribution of study population- age and sex

Age in years	Sex		Total (%)
	Male (%)	Female (%)	
<5	12 (24%)	13 (26%)	25 (50%)
5-10	10 (20%)	5(10 %)	16 (30%)
10-14	4 (8%)	6 (12%)	9 (20%)
Total	**26 (52%)**	**24 (48%)**	**50 (100%)**

Table 3 shows the study population according to age and sex. 50 children were enrolled in our study of them 50% were < 5 years, 30% were between 5-10 years, 20% were between 10-14 years. Majority of patients were below <5 years constituting around 50%

Table 2 Distribution of study population according to gender

Sex	Frequency	Percent
Male	26	52.0
Female	24	48.0
Total	**50**	**100.0**

Table 4 shows the distribution of study population according to gender. Among the study group 26 (52%) were male and 24 (48%) were female.

Table 3: Distribution of study population according to diagnosis atadmission

Diagnosis at admission	Frequency	Percent
Pneumonia	12	24.0
Meningitis	10	20.0
Pyelonephritis	8	16.0
Enteric Fever	5	10.0
Dengue Fever	4	8.0
Gastroenteritis	4	8.0
Osteomyelitis	4	8.0
Septic arthritis	3	6.0
Total	**50**	**100.0**

Children in our study were diagnosed at admission with enteric and dengue fever were 5 (10%) and 4 (8%,) followed by pneumonia were 12 (24%), meningitis 10 (20%) , pyelonephritis 8 (16%), gastroenteritis 4 (8%), osteomyelitis 4 (8%) and septic arthritis 3(6%) these were major clinical presentation in our study.

Table 4: Distribution of study population according to presentingcomplaints

Presenting Complaints	Frequency	Percent
Fever	10	20.0
Cough	7	14.0
Altered sensorium	5	10.0
Seizures	5	10.0
Swelling of limb and pain	7	14.0
Burning micturition	4	8.0
Loose stools	4	8.0
Abdominal pain	3	6.0
Haematuria	3	6.0
Vomiting	2	4.0
Total	**50**	**100.0**

The above table shows that 10 (20%) fever were followed by 7 (14%) cough, 5 (10%) in altered sensorium and seizures, 7 (14%) swelling of limb and pain, 4 (8%) both burning micturition and loose stools, 3 (6%) abdominal pain and haematuria each and 2 (4%) vomiting of children complaints were seen in this study.

Table 5 Distribution of study population according to type of sepsis

Type of sepsis	Frequency	Percent
Community AcquiredInfection (CAI)	49	98.0
Hospital Acquired Infection(HAI)	1	2.0
Total	**50**	**100.0**

Out of 50 children included in the study, 49 (98%) were CommunityAcquired Infection, 1 (2%) was Hospital Acquired Infection.

Table 6 Distribution of sepsis based on clinical severity

Distribution of sepsis basedon clinical severity	Frequency	Percent
SIRS	13	26.0
Sepsis	18	36.0
Severe sepsis	10	20.0
Septic shock	9	18.0
Total	**50**	**100.0**

Table 6 shows the distribution of sepsis based on clinical severity 13 (26%), 18 (36%), 10 (20%), 9 (18 %) of SIRS, Sepsis,Severe Sepsis & Septic Shock respectively was seen in this study

Table 7: Determination of mean and standard deviation of Totalleucocyte count, C-reactive protein and Procalcitonin

	Total leucocytecount	C- reactive protein	Procalcitonin
Mean	13635.20	46.14	11.08
Std. Deviation	7232.731	42.441	24.209

In Table 7 Average of 13635.2 ± 7232.73 total leucocyte count, 46.14 of C-reactive protein and 11.08 mean of procalcitonin were seen inthis study.

Table 8 Total leucocyte count range

Total leucocyte count	Frequency	Percent
<4000	7	14.0
4000-11000	11	22.0
>11000	32	64.0
Total	**50**	**100.0**

Among the 50 children the total leucocyte count from <4000 to >11000 per microliter of blood was studied. In this nearly 32 children werecome under > 11000.

Table 9 Descriptive analysis of Culture among study population

Culture +/-	Frequency	Percent
Positive	29	58.0
Negative	21	42.0
Total	**50**	**100.0**

Out of 50 cases, culture positive was seen in 29 (58%) cases.

Table 10 : Distribution based on Organism isolated among studysubjects

Organism isolated amongstudy subjects	Frequency	Percent
Streptococcus pneumoniae	5	10.0
Escherichia coli	6	12.0
Salmonella typhi	5	10.0
Staphylococcus aureus	5	10.0
Mycobacterium tuberculosis	2	4.0
Neisseria meningitidis	2	4.0
Hemophilus influenza	2	4.0
Klebsiella pneumoniae	1	2.0
Enterococcus	1	2.0
No growth	21	42.0
Total	**50**	**100.0**

In the above table 10 different organisms were identified in patients sample. Among 50 patients, 21 (42%) showed no growth

Table 11 Descriptive analysis of CRP among study population

Distribution of sepsis based on clinica assessment	CRP		Total
	Positive (%)	Negative (%)	
SIRS	10 (20%)	3 (6%)	13 (26%)
Sepsis	17 (34%)	1 (2 %)	18 (36%)
Severe sepsis	10 (20%)	0	10 (20%)
Septic shock	9 (18%)	0	9 (18%)
Total	**46 (92%)**	**4 (8 %)**	**50 (100%)**

Fisher's Exact Test p value=0.106

Sepsis 17 (34%), SIRS 10(20%), severe sepsis 10(20%) and septic shock9(18%) were positively associated with CRP.

Table 12 Serum Procalcitonin range based on clinical severity ofsepsis

Distributionof sepsis based on clinical assessmen	Serum Procalcitonin range (ng/ ml)				Total
	< 0.5	> 0.5 & > < 2	> 2 & > < 10	> 10	
SIRS	7 (53.8%)	5 (38.4 %)	1 (7.7%)	0	13 (100%)
Sepsis	1 (5.6%)	4 (22.2%)	13 (72.2%)	0	18 (100%)
Severesepsis	0	0	10 (100%)	0	10 (100%)
Septicshock	0	0	1 (11.1%)	8 (88.9%)	9 (100%)
Total	**8**	**9**	**25**	**8**	**50**

Table 13 Descriptive analysis of Procalcitonin among study population

Distribution of sepsis based on clinical assessment	PCT		Total
	Positive	Negative	
SIRS	2 (4%)	11 (22%)	13 (26%)
Sepsis	15 (30%)	3 (6%)	18 (36%)
Severe sepsis	10 (20%)	0	10 (20%)
Septic shock	9 (18%)	0	9 (18%)
Total	**36 (72%)**	**14 (28%)**	**50 (100%)**

Fisher's Exact Test p value=0.0001

Sepsis 15 (30%), SIRS 2 (4%), severe sepsis 10(20%) and septic shock 9(18%) were positively associated with procalcitonin levels

Table 14 Descriptive analysis of serial Procalcitonin

	PCT		p value (ANOVA)
	Mean	Std. Deviation	
D 1 (n=20)	22.9660	35.30358	0.664
D 2 (n=20)	21.7400	36.86609	
D 3 (n=20)	14.0975	27.54278	

Table 15 Prediction of mortality based on Serial Procalcitoninamong study population

Outcome		DI PCT (n =20)	D3 PCT (n=20)	D5 PCT (n=20)
Survivors (n =17)	**Mean**	**9.489**	**7.929**	**3.526**
	SD	**13.90**	**16.21**	**8.62**
Non survivors(n= 3)	**Mean**	**99.3**	**100**	**74**
	SD	**1.154**	**0**	**16.70**

P value: <0.0001

In the above table, serial procalcitonin level was seen in bothsurvivors and non survivors. Serial PCT mean level was observed high (99.3) in mortality cases. The difference was statistically significant

Table 16 Predictive validity of biomarkers in Septic Shock amongstudy population

Test Result Variable(s)	Area	95% ConfidenceInterval		P value
		Lower Bound	Upper Bound	
TLC	**.822**	**.651**	**.994**	**.088**
CRP	**.625**	**.410**	**.839**	**.110**
PCT	**.993**	**.976**	**1.000**	**.009**

	Cut off value	Sensitivity	Specificity
TLC	**16050.0**	**88.9%**	**75.6%**
CRP	**16.0**	**88.9%**	**24.4%**
PCT	**8.50**	**88.9%**	**95.1%**

Among 50 patients, the validity of PCT, CRP and total leucocyte count of biomarkers in Septic Shock with cut off values, sensitivity and specificity were calculated which was not statistically significant

Table 17 Predictive validity of biomarkers in Severe Sepsis amongstudy population

Test ResultVariable(s)	Area	95% Confidence Interval		P value
		LowerBound	Upper Bound	
TLC	**.605**	**.428**	**.782**	**.308**
CRP	**.515**	**.317**	**.713**	**.884**
PCT	**.724**	**.584**	**.863**	**.030**

	Cut off value	Sensitivity	Specificity
TLC	**11900.0**	**80%**	**40%**
CRP	**16.0**	**90%**	**25%**
PCT	**3.50**	**90%**	**72.5%**

Among 50 patients, the validity of PCT, CRP and total leucocyte count of biomarkers in severe sepsis with cut off values, sensitivity and specificity were calculated which was not statistically significant.

Table 18 Predictive validity of biomarkers in Sepsis among studypopulation

Test Result Variable(s)	Area	95% ConfidenceInterval		P value
		LowerBound	UpperBound	
TLC	**.376**	**.215**	**.537**	**.148**
CRP	**.445**	**.287**	**.603**	**.524**
PCT	**.400**	**.240**	**.560**	**.245**

	Cut off value	Sensitivity	Specificity
TLC	4200.0	83.3%	15.6%
CRP	14.0	83.3%	21.9%
PCT	0.50	83.3%	34.4%

Among 50 patients, the validity of PCT, CRP and total leucocyte count of biomarkers in sepsis with cut off values, sensitivity and specificitywas calculated which was not statistically significant

Table. 19 Predictive validity of biomarkers in SIRS among studypopulation

Test Result Variable(s)	Area	95% Confidence Interval		P value
		Lower Bound	Upper Bound	
TLC	.314	.162	.466	.048
CRP	.457	.243	.672	.650
PCT	.055	.000	.117	.000

	Cut off value	Sensitivity	Specificity
TLC	**3350.00**	**76.9%**	**8.1%**
CRP	**11.50**	**69.2%**	**5.4%**
PCT	**.50**	**15.4%**	**8.1%**

Among 50 patients, the validity of CRP and total leucocyte count ofbiomarkers in SIRS with cut off values, sensitivity and specificity were calculated which was not statistically significant. But in procalcitonin showed highly significant than other parameters

DISCUSSION

Several studies have reported that 5% to 30% of pediatric sepsis will develop septic shock and mortality will occur in more than 50% of children with septic shock [4]. However, there is lack of Indian studies on mortality in paediatric sepsis. PCT concentrations were detected at a significantly higher frequency among 116 patients with severe sepsis. Therapy based on values can target severe cases and aid the physician in managing severely septic patients.

Hence there is need to define the role of serum procalcitonin in paediatric sepsis, as there are lack of studies assessing serum PCT in paediatric sepsis. Therefore, we conducted a study to evaluate diagnostic efficacy of Procalcitonin as biomarker and use of Procalcitonin in prognosticating sepsis in children.

Present study was conducted One year from January 2019 to January 2020 and we enrolled children aged between 2 months to 14 years. Our sample size was 50 patients. In our study, 50 children were enrolled with clinical suspicion of sepsis.

Similar study done by Juan casado –flores et al showed that frequency of shock (p=.05) and MODS (p=.06) was slightly higher in children <1-year-old (45% and 36% in children <1-year-old, 31 and 35% in old children > 4-year-old) [8]. Militaru and Martinovici showedthat age influences the epidemiology of sepsis. Infants and older children (age 1 month to 18 years) are two epidemiologically distinct paediatric populations, with different incidences, underlying diseases, sites of infection, infecting organisms, and organ dysfunction [7]. Our study was consistent with previous studies we found majority of children with sepsisless than 5 years.

In the present study groups the validity of sepsis, SIRS, septic shockand severe sepsis with PCT levels were positive in 36 children. Receiver operating characteristics (ROC) curves for our studied sepsis markers revealed that serum PCT levels the cut off value of 0.50 ng/ml, 0.50 ng/ml, 8.50 ng/ml and 3.50 ng/ml offered diagnostic sensitivity of 83.3%, 15.4%,88.9 %, and 90% specificity 34.4%, 8.1%, 95.1% and 72.5% values. Among this SIRS, PCT level compared to CRP and total leucocyte count sensitivity and specificity was less that's why it showed statistically significant than others. PCT could be used as a diagnostic marker in severity of sepsis in paediatric age group.

CONCLUSION

There is a positive association between serum procalcitonin levels, CRP and total leucocyte count and severity of sepsis. Sensitivity and specificity of procalcitonin was high in sepsis, septic shock and severe sepsis. Based on the result, Procalcitonin can be used as a diagnostic marker of severity of sepsis. Procalcitonin levels were high in sepsis, septic shock and severesepsis and there was a positive association between serum procalcitonin levels and severity of sepsis. SIRS is negatively associated with Positive serum procalcitonin. Serum procalcitonin levels are positively associated with positive serum CRP. Procalcitonin levels were higher in the mortality group. As procalcitonin levels increases mortality also increases. Procalcitonin can be used as a diagnostic marker of severity of sepsis. PCT in paediatric sepsis diagnosis will be useful in starting antibiotics as early as possible and limiting the unnecessary use of antibiotics, which affects the development of resistant bacteria. This wouldbe useful in reducing the number of intensive care admission, shortening hospital stay, and increasing the availability of hospital beds, which are very important issues, especially in developing countries with limited facilities.

REFERENCES:

1. Rafael, sierra. C. (2007) - reactive protein and Procalcitonin as markers of infection, inflammatory response, and sepsis. Clin pulm Med 14:127-139.
2. Liliana, simon., Patrick saint Louis., Devendra, K., Amre, Jacques, Lacoix., France, Gauvin. (2008) Procalcitonin and C-reactive protein as markers of bacterial infection in critically ill children at onset of systemic inflammatory response syndrome. Pediatrcriti care Med; 9:407-413.
3. Martin GS, Mannino DM, Eaton S, Moss M. (2003). The epidemiology of sepsis in the United States from 1979 through 2000. N Eng J Med; 348:1546-54.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, CarcilloJ, Pinsky MR et al. (2001). Epidemiology of severe sepsis in the UnitedStates: analysis of incidence, outcome, and associated costs of care. Crit Care Med; 29:1303-10.
5. S Todi, S Chatterjee and M Bhattacharyya. (2007). Epidemiology of severe sepsis in India. Critical Care; 11: 6
6. Muller B,Becker KL,Schachinger H,Rickenbacher P R, Huber PR,Zimmerli W etal. (2000).Calcitonin precursors are reliable markers of sepsis in a medical intensive careunit. Crit Care Med;28:977-983.
7. Oberhoffere M,Ruwurm S,Bredle D Chatzinicolau K,Reinhart K.(2000). .Discriminative power of inflammatory markers for prediction of tumor necrosis factor-alpha, interleukin -6 in patients with systemic inflammatory syndrome (SIRS) or sepsis at arbitrary points. Intensive Cara Medicine;26:170-174.
8. Selberg O,Hecker H,Martin M,Klos A,Bautsch W,Kohl J.(2000). Discrimination of sepsisand systemic inflammatory syndrome by determination of circulating plasma concentration of procalcitonin, protein complement 3a, and interleukin-6. Crit Care Med; 28:2793-2798. 130
9. Suprin E,Campus C,Gacouin A,Le Tulzo Y,Lavoue S,Feuillu A,Thomas R. (2000).Procalcitonin: a valuable indicator of infection ina medical ICU? Intensive care medicine; 26:148-152.
10. Novosad SA, Sapiano MRP, Grigg C, et al. (2016). Vital signs: epidemiology of sepsis: prevalence of health care factors and opportunities for prevention. Morb Mortal Wkly Rep.;65(33):864–869. doi: 10.15585/mmwr.mm6533e1.

11. Vincent J-L, Rello J, Marshall J, et al.(2009). International study of the prevalence and outcomes of infection in intensive care units. JAMA.;302(21):1303–1310. doi: 10.1001/jama.2009.1754.
12. Gül F, Arslantaş MK, Cinel I, et al.(2017). Changing definitions of sepsis. Turk J Anaesthesiol Reanim; 45(3): 129–138.