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Role of Procalcitonin after Paediatric Cardiac Surgery Under Cardiopulmonary Bypass and Its Correlation with Other Marker of Inflammation

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Abstract

Objective: The effect of Cardiopulmonary bypass on serum Procalcitonin, and its correlation with other markers of inflammation in paediatric cardiac surgery patients. ***Design:*** A prospective observational study. ***Subjects/Patients:*** 52 paediatric patients requiring cardiac surgery under Cardiopulmonary bypass. ***Methods:*** Serum Procalcitonin, C-reactive protein and Total leukocyte count levels were measured preoperatively as baseline and then postoperatively on day 1, 3 and 5. Their kinetics and correlations were evaluated. ***Results:*** Peak levels of Procalcitonin showed a positive correlation with duration of Cardiopulmonary bypass time (rho=0.316, p= 0.02), aortic cross clamp time (rho=0.319, p=0.021), length of Intensive care unit stay (rho=0.418, p= 0.002). No correlation was observed between duration of Cardiopulmonary bypass or aortic cross clamp time and length of Intensive care stay with C-reactive protein or Total leukocyte count levels. Procalcitonin exhibits faster kinetics as compared to C-reactive protein and Total leukocyte count. ***Conclusions:*** Serial Procalcitonin measurements may be useful for identifying infections in the later post-operative period. However, Procalcitonin may not be considered an ideal biomarker for post-operative infections in paediatric cardiac surgery under Cardiopulmonary bypass, warranting further research.

Keywords: ***Biomarker, Cardiac surgery, Cardiopulmonary bypass, Paediatrics, Procalcitonin***

Introduction

Cardiopulmonary bypass (CPB) is a modality of controlled circulation which is an integral part of majority of cardiac surgery. CPB induces a non-specific generalized systemic inflammatory response syndrome (SIRS) also referred to as systemic inflammatory response after bypass (SIRAB) as does any bacterial infection [1]. Due to this non-specific inflammatory state observed post-operatively after CPB, the traditional tests to detect infection are unreliable in this subset of patients [2-7]. Thus, this non-specific SIRS after CPB may act as a confounding factor while diagnosing post-operative infection.

Here comes the role of biomarkers. Biomarkers can be used to differentiate sepsis from non-infective causes of SIRS. Biomarkers may be used either as a diagnostic or prognostic marker or both. Procalcitonin (PCT) is proposed as a specific marker of bacterial infection in particular [8]. C-reactive protein (CRP) on the other hand is non-specific [9]. However, PCT has been shown to be affected by CPB in adult patients. Thus, the utility of PCT in patients post CPB is questionable. Several studies have been conducted in the adult population [10-14]. to assess its utility as means of sepsis biomarker with conflicting results.

Paediatric patients are known to produce profound SIRS after CPB [15,16]. Therefore, PCT may be affected to a large extent

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after paediatric cardiac surgery under CPB. Further, studies in paediatric patients are scarce related to this subject, and accurate role (diagnostic or prognostic or both) of PCT after paediatric cardiac surgery under CPB is not well established [17]. Delay in diagnosis and treatment of sepsis post-operatively can lead to increased morbidity mortality and mortality, especially in paediatric patients.

With this background, we studied the effect of CPB on PCT and other biomarkers, to identify the actual role of PCT in post-operative period after paediatric cardiac surgery under CPB.

Methods

This study was carried out after institutional ethical committee approval and informed consent of the parent/ guardian of paediatric patient. The patient or their relatives were informed of the risks and benefits of the study.

A prospective observation study was carried out on consecutive paediatric patients requiring elective cardiac surgery under CPB during the period August 2017 to July 2018.

All these patients were screened to assess their suitability for inclusion into the present study, according to the inclusion and exclusion criteria, and a total of 52 patients were enrolled in the study once they met these requirements.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Paediatric patients up to 14 years of age requiring elective cardiac surgery under CPB.

Exclusion Criteria

- Patients with preoperative SIRS of any cause (infection, systemic disease).
- Patients on immunosuppressive therapy e.g. corticosteroids, chemotherapy.
- Non-steroidal anti-inflammatory drug use within the last seven days before surgery.
- Patients requiring emergency surgery.
- Patients who were unwilling to give consent.

A standard anaesthesia technique was used in all the patients. Patients were premedicated with 0.5 mg/kg of midazolam orally 30 minutes prior to taking them to operating room (OT). Inside the OR, standard ASA monitoring including five lead electrocardiography (ECG), pulse oximetry and non-invasive blood pressure (NIBP) were applied. Anaesthesia was induced with 8% sevoflurane with 100% oxygen using a circle system. Peripheral venous line was secured followed by intravenous administration of fentanyl 3-5 µg/kg/body weight and vecuronium 0.1 mg/kg to facilitate endotracheal intubation. Invasive arterial pressure monitoring access and central venous access was secured after induction of general anaesthesia. Anaesthesia was maintained during whole of the period including cardiopulmonary bypass duration with isoflurane, intravenous morphine (intermittent boluses; total 0.5 µg/kg during surgery and vecuronium boluses. All patients were operated under standard cardiopulmonary bypass according to institutional protocol. A standard anticoagulation technique was used for all the patients before cannulation. Heparin 4 mg/kg was given for achieving activated clotting time (ACT) more than 480 seconds. During bypass, ACT's were obtained every hour, to determine adequacy of anticoagulation. Myocardial protection was performed with intermittent infusion of Delnido cardioplegia Intraoperatively, IV Milrinone 0.3-0.7 µg/kg/min and IV Noradrenaline 0.05- 0.2 µg/kg/min were infused to facilitate weaning from CPB. All patients were shifted to cardiac surgical intensive care unit (ICU) after surgery. For antimicrobial prophylaxis cefuroxime was given at the induction as per paediatric dose and repeated every four hours during surgery. Decisions regarding extubation and inotrope support were left to attending intensivist.

After operation, clinical assessment, including body temperature, microbiological and radiological examinations were done as suggested by clinical condition of the patient.

PCT was measured preoperatively on the day of surgery before shifting to OT as baseline and then postoperatively on post-op day (POD) 1, 3 and 5.

PCT was measured by Electrochemiluminescence (ECLIA) using the Elecsys BRAHMS PCT test (Roche Diagnostics, Mannheim, Germany) (normal range: 0.01-0.5 ng/ml). Serum CRP concentrations were measured by Immunoturbidimetry on Siemens ADVIA 1800 chemistry system analyser (Siemens Healthcare Diagnostics Inc.) (normal range: 0.05-0.35 mg/dL).

Other routine investigations were sent as suggested by clinical condition of the patient. Patients were followed up to look for any complications, length of ICU stay, re-operation.

Statistical Analysis

The study was carried out in a prospective observational manner and statistical analysis of the data was done at the end of the study using appropriate statistical tests depending upon the variables. Quantitative data was calculated as mean ± SD and range or median and interquartile range, or 1st-3rd quartile value as appropriate. Normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of normality. For normally distributed data, means were compared using independent t-test. For skewed data or scores, Mann-Whitney U-test was applied. For discrete categorical data, number and percentages were calculated. Chi-Square test or Fisher's Exact test were applied for categorical data. Pearsons / Spearman's correlation were used as appropriate to assess the correlation between various parameters. For time related data, the Repeated Measure ANOVA was applied to see the trend of parameter mean values over the two groups.

All statistical tests were two-sided. A P value of <0.05 was considered to indicate statistical significance. Analysis was conducted using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL, USA).

Data is presented as median (1st- 3rd quartile value) in the text and as a box plot (25th percentile, 50th percentile, 75th percentile; with whiskers extending to 95% confidence intervals) in figures, unless otherwise mentioned.

Results

Demographic and diagnostic profile

The median age was 42 months (12-105). Rest of the demographic data, diagnostic profile and intra-operative and peri-operative details of our study population are represented in table I, table II, table III and table IV.

Post-operative details

In post-operative period, complications were observed in 9 (17.3%) out of total 52 patients. Most common complication observed was lung collapse (in 7 patients) which responded well to conservative management. One patient had complete heart block for which permanent pacemaker was implanted. One patient had air embolism which responded well to conservative management, with no neurological deficit. Thus, most of the complications were minor (lung collapse) which responded well to conservative management. There was no mortality in the study population. The mean ICU stay

was 5.37 days +/- 2.82 SD. Seventeen patients required microbial cultures during the study, however all were sterile. All patients in the study period were free of sepsis in peri-operative period.

Biomarkers

Procalcitonin (PCT)

Serum PCT values were in normal range in all patients before surgery (baseline). PCT values increased from median of 0.29 ng/ml (0.08-0.35) pre-operatively to 8.8 ng/ml (2.63-23.61) at POD1; 4.58 ng/ml (1.53-9.23) at POD 3; and 1.08 ng/ml (0.45-2.27) at POD 5, as depicted in the box-plot (**Figure 1**).

The PCT value peaked at POD 1, in 90.4% of patients (47 out of 52 patients) whereas at POD 3, the peak value of PCT was attained by only 9.6% of the patients (5 out of 52 patients). At POD 5, the peak value of PCT was attained by none of the patients. Hence, PCT value peaks in majority (90.4%) of patients at POD 1 as depicted in the bar chart (**Figure 2**).

On pair-wise comparisons of PCT values on subsequent collection days, it was observed that the increase in PCT value from baseline to POD1 was highly significant ($p<0.0001$); the decrease in PCT value from POD 1 to POD 3 was not significant ($p= 0.197$); the decrease in PCT value from POD 3 to POD 5 was significant ($p=0.005$). Further, PCT value at POD 5 did not reach baseline and was significantly higher than the baseline (pre-operative) PCT value ($p=0.018$).

To summarize, PCT values reached maximum value by POD 1, then declined sharply at POD 3 and further declined significantly at POD 5, but still remained significantly above the baseline at POD 5, as depicted in the trend chart of PCT (**Figure 3**).

C-reactive protein (CRP)

Serum CRP values were in normal range in all patients before surgery (baseline). CRP values increased from median of 0.16 mg/dL (0.11-0.19) pre-operatively, to 7.29 mg/dL (4.7-34) at POD 1; 14.64 mg/dL (7.56-31.28) at POD 3; and 6.47 mg/dL (3.66-20.2) at POD 5, as depicted in the box-plot (**Figure 4**).

The CRP value peaked at POD 1, in 32.7% of patients (17 out of 52 patients) whereas at POD 3, the peak value of CRP was attained by 63.5 % of the patients (33 out of 52 patients). At POD 5, the peak value of CRP was attained by 3.8% of the patients (2 out of 52 patients). Hence, CRP value peaks in majority (63.5%) of patients at POD 3 as depicted in the bar chart (**Figure 5**).

On pair-wise comparisons of CRP values on subsequent collection days, it was observed that the increase in CRP value from baseline to POD1 was highly significant ($p<0.0001$); the increase in CRP value from POD 1 to POD 3 was not significant ($p= 1$); the decrease in CRP value from POD 3 to POD 5 was significant ($p=0.002$). Further, CRP value at POD 5 did not reach baseline and was significantly higher than the baseline (pre-operative) CRP value ($p<0.001$).

To summarize, CRP value increased at POD 1 and continued to rise till POD 3, and then started declining after POD 3, but even at POD 5 the CRP values remained significantly above the baseline, as depicted in the trend chart of CRP (**Figure 6**).

Total leukocyte count (TLC)

TLC values increased from median of 8100/µL (7600-9200) pre-operatively, to 13200/µL at POD1 (11250-15200); 13200/µL (11100-14825) at POD 3; and then declined to 9550/µL (8125-11125) at POD 5, as depicted in the box-plot (**Figure 7**).

The TLC value peaked at POD 1, in 57.7% of patients (30 out of 52 patients) whereas at POD 3, the peak value of TLC was attained by 40.38 % of the patients (21 out of 52 patients). At POD 5, the peak value of TLC was attained by 1.9% of the patients (1 out of 52 patients). Hence, TLC value peaks in majority (57.7%) of patients at POD 1. However, a good percentage of patients (40.38%) attain peak value of TLC at POD 3 as well, as depicted in the bar chart (**Figure 8**).

On pair-wise comparisons of TLC values on subsequent collection days, it was observed that the increase in TLC value from baseline to POD1 was highly significant ($p<0.0001$); the decrease in TLC value from POD 1 to POD 3 was not significant ($p= 1$); the decrease in TLC value from POD 3 to POD 5 was highly significant ($p<0.0001$). Further, TLC value at POD 5 did not reach baseline and was significantly higher than the baseline (pre-operative) TLC value ($p=0.026$).

To summarize, TLC value increased significantly at POD 1 and then declined subsequently, the change in value from POD 1 to POD 3 is insignificant, however further decline from POD 3 to POD 5 is significant. But even at POD 5, the TLC values remained significantly above the baseline, as depicted in the trend chart of TLC (**Figure 9**).

Correlations

Procalcitonin (PCT)

On statistical analysis, peak levels of PCT showed a positive correlation with:

- Duration of CPB time (rho=0.316, p= 0.02)
- Aortic cross clamp (AXC) time (rho=0.319, p=0.021)
- Length of ICU stay (rho=0.418, p= 0.002)

On statistical analysis, peak levels of PCT showed a negative correlation with:

- Lowest CPB temperature (rho= -0.327, p=0.018)

There was no significant correlation of peak PCT levels with age (p=0.457), BSA (p=0.253), and duration of mechanical ventilation (p=0.149).

Peak PCT value was more in patients with post operative complications (median = 24.04), but it was not statistically significantly greater than the PCT values in patients without post operative complications (p=0.051).

Correlation of PCT levels on subsequent post operative days is shown in table V.

Positive correlation was observed between PCT levels on POD 1, POD 3, and POD 5 with:

- Duration of CPB
- Aortic cross clamp (AXC) time
- Length of ICU stay

Negative correlation was observed between PCT levels on POD 1, POD 3 with:

- Lowest CPB temperature

C-reactive protein (CRP)

On statistical analysis (Spearman's Correlation), peak levels of CRP did not show any correlation with:

- Duration of CPB time (rho= -0.06, p= 0.673)
- Aortic cross clamp (AXC) time (rho= -0.061, p=0.67)
- Duration of mechanical ventilation (MV) (rho= -0.054, p=0.706)

- Length of ICU stay (rho=0.007, p=0.961)
- Lowest CPB temperature (rho= -0.108, p=0.444)
- Post operative complications (p=0.183)

Correlation of CRP levels on subsequent post-operative days is shown in the table VI.

No correlation was observed between CRP levels on POD 1, POD 3, and POD 5 with:

- Duration of CPB time
- Aortic cross clamp (AXC) time
- Duration of mechanical ventilation (MV)
- Length of ICU stay
- Lowest CPB temperature

Total leukocyte count (TLC)

On statistical analysis (Pearson Correlation), peak levels of TLC did not show any correlation with:

- Duration of CPB time (r= -0.054, p= 0.703)
- Aortic cross clamp (AXC) time (r= -0.025, p=0.861)
- Duration of mechanical ventilation (MV) (r= -0.054, p=0.706)
- Length of ICU stay (r=0.127, p=0.368)
- Lowest CPB temperature (r= -0.085, p=0.550)
- Post operative complications (p=0.922)

Correlation of TLC levels on subsequent post operative days is shown in table VII.

No correlation was observed between TLC levels on POD 1, POD 3, and POD 5 with:

- Duration of CPB time
- Aortic cross clamp (AXC) time
- Duration of mechanical ventilation (MV)
- Length of ICU stay

Negative correlation was observed between TLC levels on POD 5 with CPB temperature.

Table I: Sex distribution of study population

Sex	Number of patients	Percentage (%)
Male	33	63.5
Female	19	36.5
Total	52	100.0

Table II: Demographic profile of study population

	Mean	Median	1st-3rdQuartile	Range
Height (cm)	98.27 +/- 28.98	94.5	69.5-125.75	60-151
Weight (kg)	13.6 +/- 9.08	10.15	6.775-19	3-39
BSA (kg/m^2)	0.59 +/- 0.289	0.505	0.35-0.81	0.2-1.3

Table III: Diagnostic profile of the study population

Diagnosis	Number of patients	Percentage (%)
TOF	15	28.8
VSD	14	26.9
ASD	5	9.6
DORV + VSD + PS	3	5.8
Supracardiac TAPVC	3	5.8
ASD+VSD	2	3.8
CS-TAPVC	2	3.8
AVCD	2	3.8
d-TGA	2	3.8
PAPVC	1	1.9
cc-TGA	1	1.9
Truncus I	1	1.9
Cor-triatum sinister	1	1.9
Total	52	100.0

Table IV: Intra-operative and peri-operative details

	Mean	Median	1st-3rdQuartile	Range
CPB Duration (minutes)	125.81 +/- 52.934	120.50	81.75-165	56-244
AXC Time (minutes)	89.02 +/- 42.889	88.5	49.5-111	22-185
CPB temperature ©	32.7 +/- 2.394	33	31.6-34.08	27-37
Mechanical Ventilation (MV) duration (hours)	17.24 +/- 17.516	13.5	6-20	2-112

Table V: Correlation of PCT levels postoperatively (Rho value- Correlation coefficient)

Variables	Spearman's correlation	PCT levels		
		POD 1	POD 3	POD 5
CPB time	rho value	0.378	0.363	0.349

	p value	0.006	0.008	0.011
	Correlation	**Positive**	**Positive**	**Positive**
AXC time	rho value	0.380	.0.348	0.315
	p value	0.005	0.011	0.023
	Correlation	**Positive**	**Positive**	**Positive**
MV duration	rho value	0.211	0.215	0.271
	p value	0.133	0.125	0.052
	Correlation	Not significant	Not significant	Not significant
CPB temperature	rho value	-0.350	-0.319	-0.219
	p value	0.011	0.021	0.119
	Correlation	**Negative**	**Negative**	Not significant
Length of ICU stay	rho value	0.342	0.439	0.497
	p value	0.013	0.001	0.000
	Correlation	**Positive**	**Positive**	**Positive**

Table VI: Correlation of C-Reactive Protein levels postoperatively (Rho value- Correlation coefficient)

Variables	Spearman's correlation	**CRP levels**		
		POD 1	**POD 3**	**POD 5**
CPB time	rho value	0.002	-0.007	0.03
	p value	0.988	0.959	0.832
	Correlation	No significant correlation	No significant correlation	No significant correlation
AXC time	rho value	0.004	-0.035	0.015
	p value	0.980	0.803	0.918
	Correlation	No significant correlation	No significant correlation	No significant correlation
MV duration	rho value	0.071	-0.016	0.003
	p value	0.616	0.913	0.983
	Correlation	No significant correlation	No significant correlation	No significant correlation
CPB temperature	rho value	-0.122	-0.153	-0.043
	p value	0.389	0.279	0.763
	Correlation	No significant correlation	No significant correlation	No significant correlation
Length of ICU stay	rho value	0.068	0.002	0.023
	p value	0.631	0.989	0.871
	Correlation	No significant correlation	No significant correlation	No significant correlation

Table VII: Correlation of Total Leukocyte Count levels postoperatively

Variables		**TLC levels**		
		POD 1	**POD 3**	**POD 5**
CPB time	r value	-.131	.027	.231
	p value	.354	.847	.099
	Correlation	No significant correlation	No significant correlation	No significant correlation
AXC time	r value	-.122	.068	.246
	p value	.390	.631	.079
	Correlation	No significant correlation	No significant correlation	No significant correlation
MV duration	rho value	-0.150	0.083	0.146
	p value	0.289	0.561	0.303
	Spearman's Correlation	No significant correlation	No significant correlation	No significant correlation
CPB temperature	r value	-.022	-.170	-.398
	p value	.875	.227	0.004
	Correlation	No significant correlation	No significant correlation	**Negative correlation**
Length of ICU stay	r value	.059	.067	.200
	p value	.678	.636	.156
	Correlation	No significant correlation	No significant correlation	No significant correlation

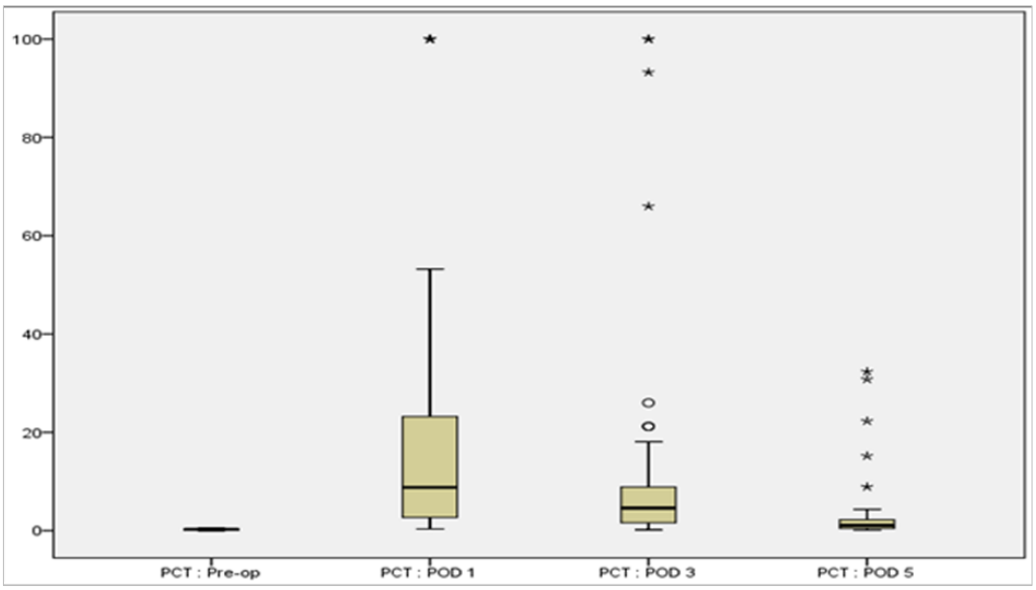

Figure 1: Boxplot showing PCT values in paediatric cardiac surgery patients under CPB. (The boxes extend from the 25th to 75th percentile, with the horizontal line at the median. Whiskers extend down to 95% confidence interval).

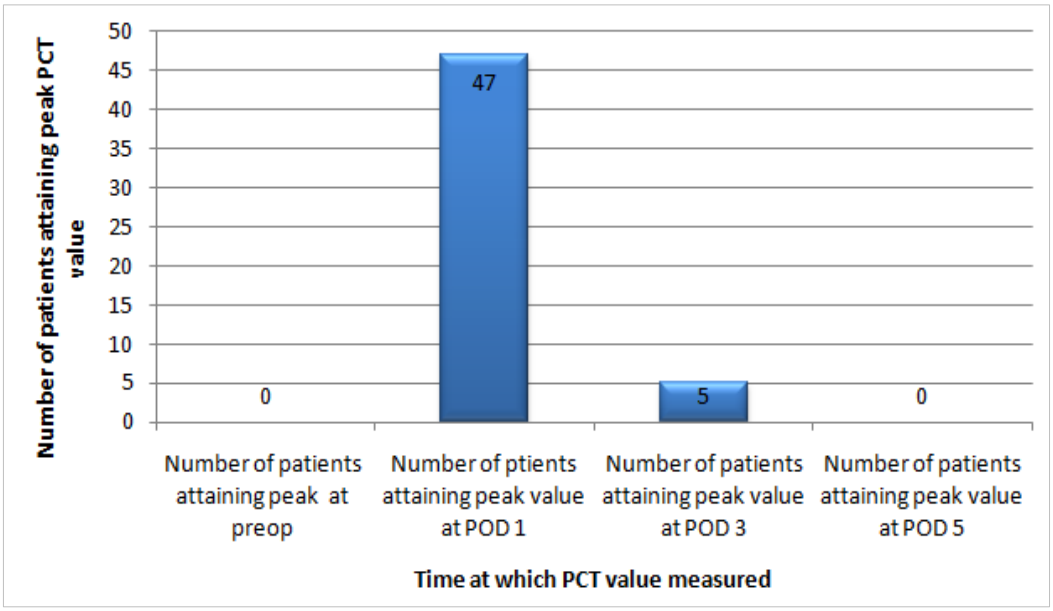

Figure 2: Bar chart depicting the number of patients who attained peak PCT values at subsequent post-operative days.

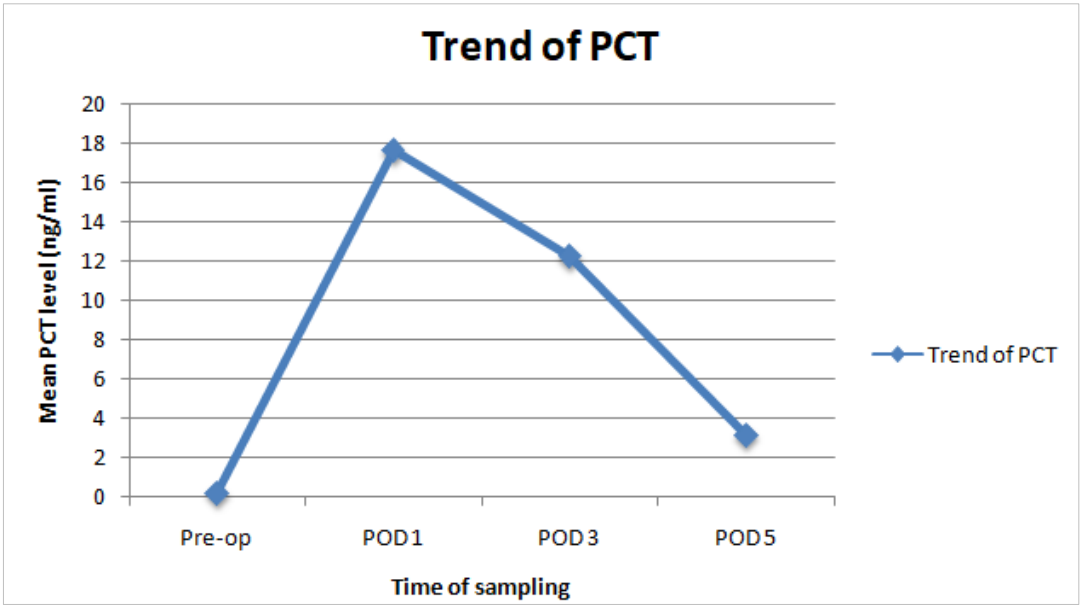

Figure 3: Post-operative trend of PCT value.

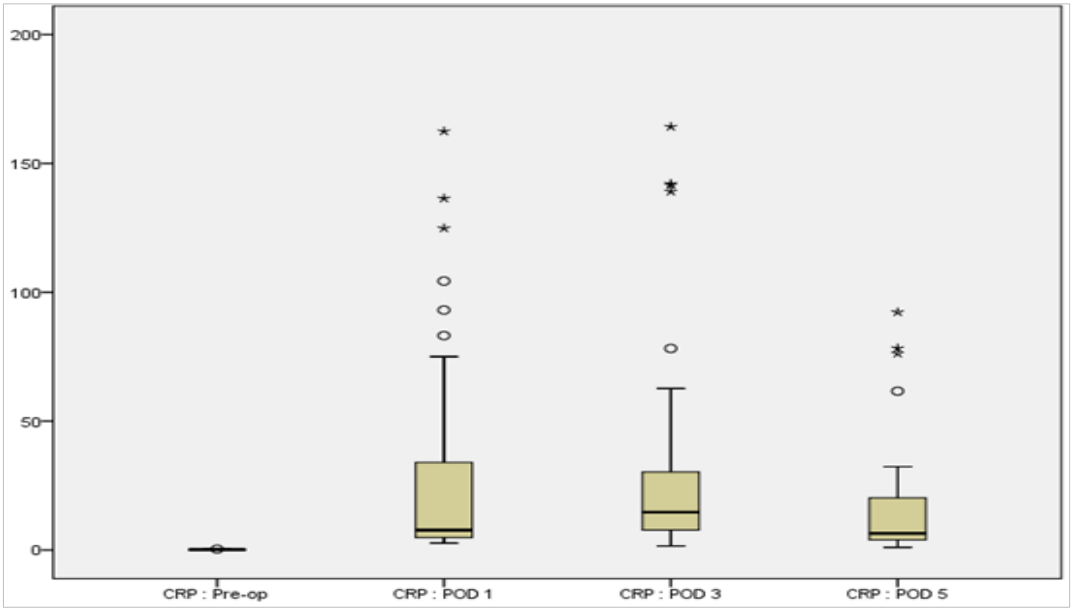

Figure 4: Boxplot showing CRP values in paediatric cardiac surgery patients under CPB. (The boxes extend from the 25th to 75th percentile, with the horizontal line at the median. Whiskers extend down to 95% confidence interval).

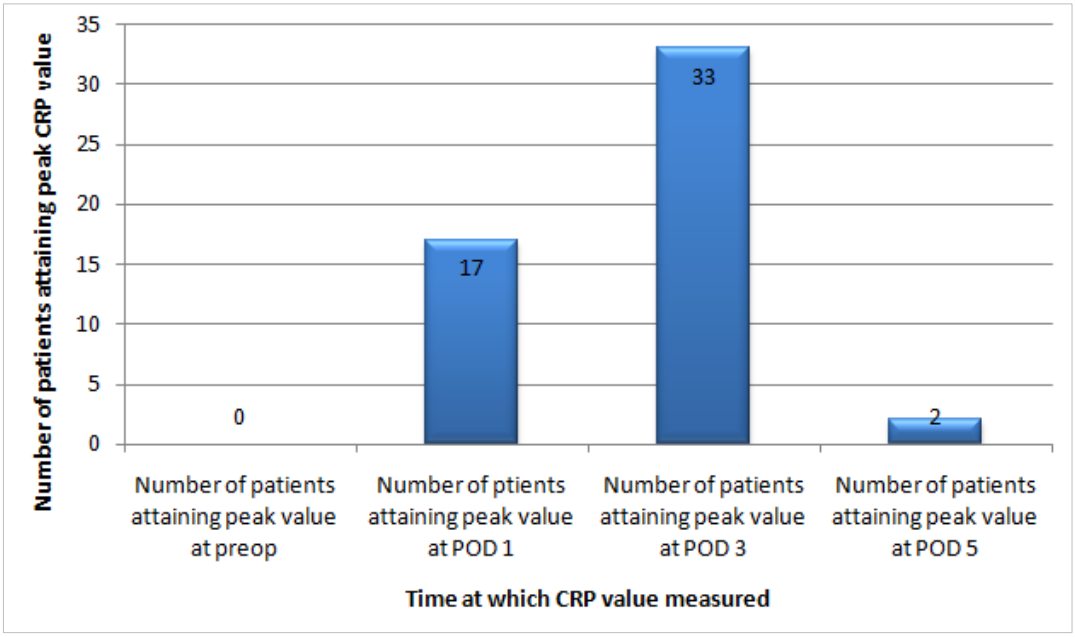

Figure 5: Bar chart depicting the number of patients who attained peak CRP values at subsequent post-operative days.

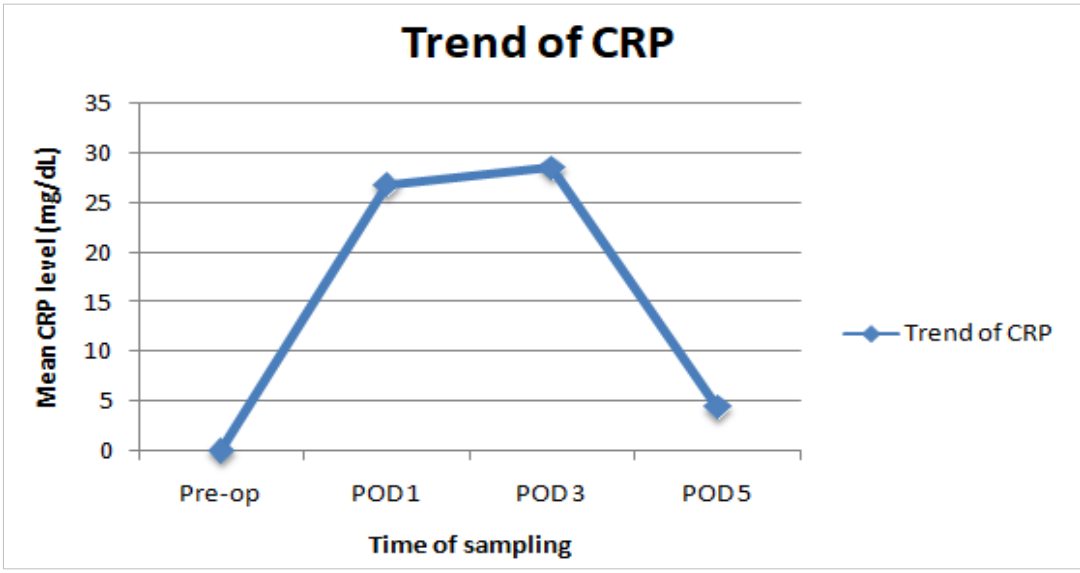

Figure 6: Post-operative trend of CRP value.

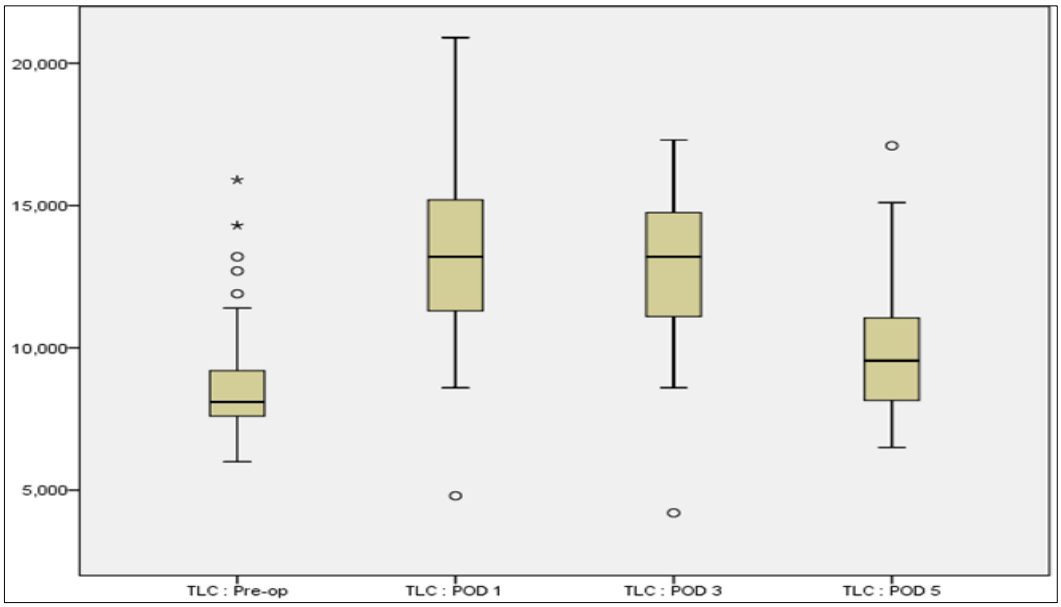

Figure 7: Box-plotshowingTLC values in paediatric cardiac surgery patients under CPB.
(The boxes extend from the 25th to 75th percentile, with the horizontal line at the median. Whiskers extend down to 95% confidence interval)

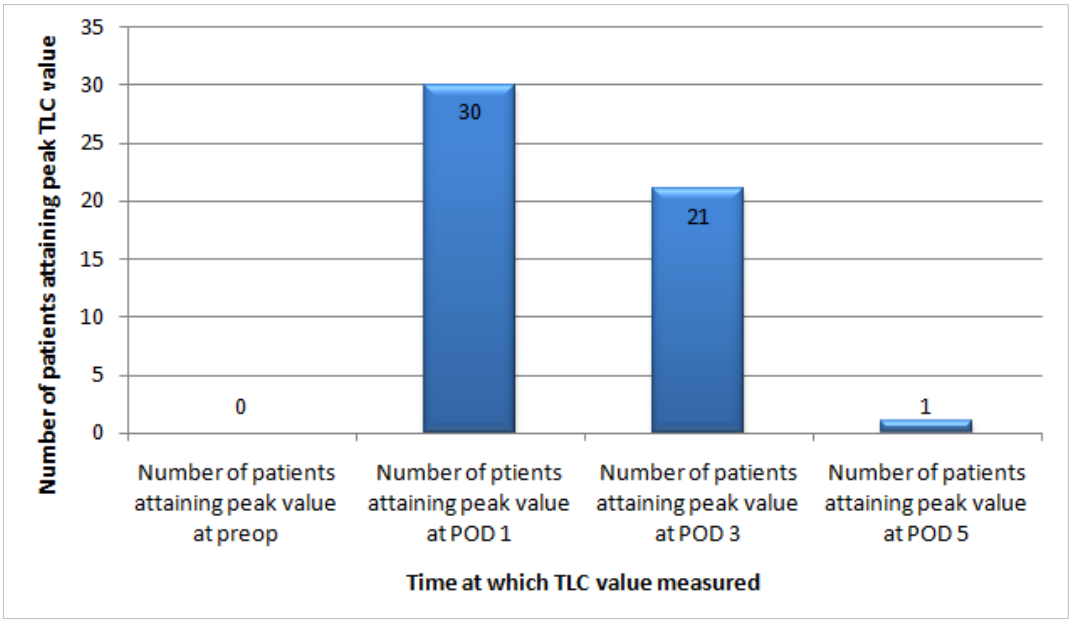

Figure 8: Bar chart depicting the number of patients who attained peak TLC values at subsequent post-operative days.

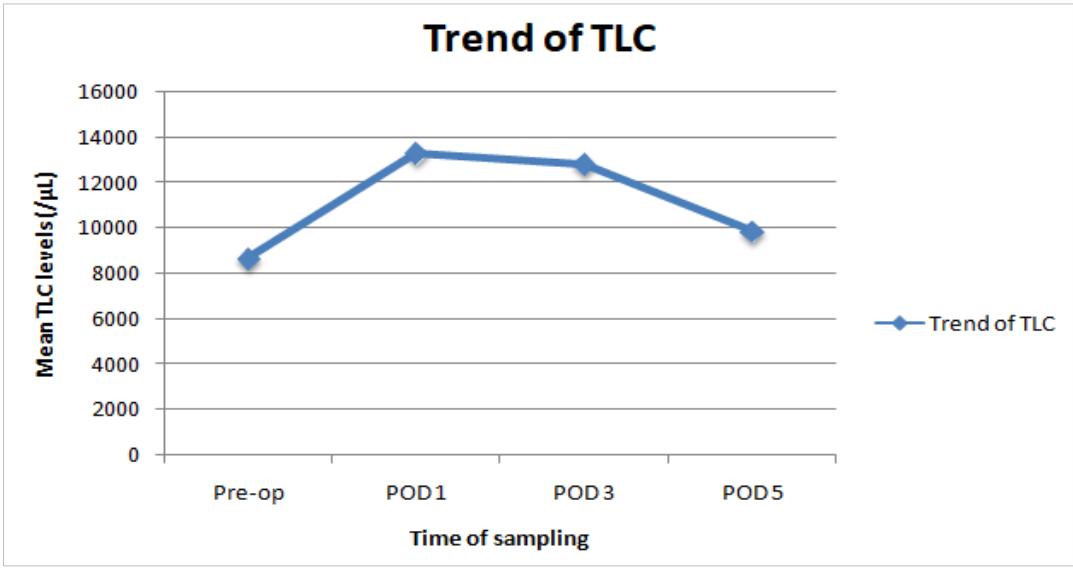

Figure 9: Post-operative trend of TLC values.

Discussion

Cardiac surgery and CPB are potent inducers of SIRS [18]. Therefore; it is challenging to differentiate sepsis from non-infective SIRS in this set of populations. Recently, PCT has been advocated as a useful diagnostic marker of infection in such a scenario [14,19-23].

Proponents of using PCT as a diagnostic marker of infection, in the post CPB scenario, cite its reason to be kinetics of PCT. PCT rises rapidly, attains an early peak (following exposure), and declines rapidly (following successful treatment or removal of trigger). These faster kinetics of PCT makes it a better biomarker than CRP or TLC (which has slower kinetics) [3,5-7,24]. in differentiating sepsis especially after CPB. These studies were conducted in older children after cardiac surgery [4,5]. We also observed that PCT peaked at POD 1, then declined sharply after POD 1, however it failed to reach baseline till POD 5, remaining significantly above it (**Figure 3**). In our study, kinetics of CRP and TLC differed from that of PCT in that, CRP and TLC levels started falling after POD 3, thus have slower kinetics (Figure 6 and 9 respectively). Our findings are similar to a recent study, which too observed that PCT has faster kinetics as compared to CRP or TLC [25]. Slower kinetics of CRP were similarly observed in a recent study which concur with our findings [26].

CPB per se should not influence PCT levels if it were to be of any value as diagnostic marker of sepsis in post CPB scenario. The very fact was demonstrated by Boeken et al [27]. This observation further reinstated the usefulness of PCT as a diagnostic marker of infection in post CPB period.

On the contrary, PCT was shown to be influenced by CPB in other studies. They observed that PCT peaks 24 hours postoperatively and returns back to baseline within 1 week. They concluded that following the trend of PCT is more important in post CPB scenario rather than an absolute value [5,13,22]. This emphasizes the role of serial PCT measurements.

Recent studies have concluded that PCT may help to rule out infection in post operative period in patients undergoing cardiac surgery under CPB [14,20]. However, it is imperative to mention here that even in these studies, PCT was found to be influenced by CPB in early post operative period. Hence, they have concluded that PCT may have a role in late post operative period. Furthermore, even in these studies only the negative predictive value of PCT to rule out infection has been identified, rather than its positive predictive value to support its role as an aid in establishing a diagnosis of infection. Therefore, even these studies concluded that PCT may have a role only to rule out infection. On the contrary, another recent study studied the kinetics of various biomarkers including PCT, CRP, TLC in post operative period after congenital heart surgery under CPB. They concluded that none of these biomarkers are reliable to differentiate infection from post operative inflammation in this subset of patients [25].

Further, SIRS after cardiac surgery per se (without CPB) has been observed to affect PCT levels [28]. This fact again raises doubts about its utility in cardiac surgery patients.

It is unclear whether PCT is useful in younger cardiac surgery patients post bypass. Several studies have included neonates and infants, but always in combination with older children. Younger patients have immature immune responses, undergo more complex surgeries, requiring prolonged CPB and AXC time [3,4,7,29-32]. All these factors produce a profound inflammatory response which may affect PCT levels.

We observed that peak PCT levels have a positive correlation with CPB time, AXC time, length of ICU stay, and negative correlation with lowest temperature of bypass. Similar correlation was observed on POD 1, POD 3 and POD 5. No correlation was observed between the duration of CPB or AXC time, length of ICU stay, MV duration and CRP or TLC levels on any subsequent postoperative days till day 5 (POD 1, POD 3, POD 5).

Several studies have been conducted to study the effect of CPB on paediatric population. They observed that PCT levels have positive correlation with CPB time, AXC time, length of ICU stay and MV duration [7,29,33]. They further demonstrated rapid kinetics in pediatric population like in adults, demonstrating superiority of PCT over CRP as a diagnostic marker of infection. Similar findings were observed in a review article which concluded that PCT is superior to CRP as a biomarker to diagnose infection in post operative period after congenital heart surgery under CPB [34].

Thus, we conclude that PCT levels are influenced positively by the duration CPB and AXC time. The positive correlation between PCT levels and CPB duration is related to non-pulsatile blood flow during the bypass. The longer the CPB duration, greater is duration of non-pulsatile blood flow, which leads to disruption of intestinal mucosal barrier, thus facilitating bacterial translocation into blood stream. This results in endotoxemia, and endotoxin is potent stimulus for PCT production [35,36]. Similar findings were replicated in other study as well, which attribute elevated PCT levels post cardiac surgery under CPB as a marker of nonobstructive mesenteric ischemia [37].

We observed that patients with higher peak and post operative PCT levels had a longer ICU stay. Celebi et al. also observed similar findings [6]. Zant et al also concluded that elevated PCT levels postoperatively as an indicator of adverse outcome after cardiac surgery [38]. Hence, we believe that higher peak PCT levels and post-operative PCT levels can predict prolonged ICU stay, thus acting as a prognostic marker.

The trend of PCT levels in paediatric cardiac surgery patients is similar to adult population but the absolute PCT values are slightly higher than that observed in adult patients. PCT levels were slightly higher postoperatively in our study because we studied paediatric patients. This can be hypothesized to be due to the relatively higher SIRS in pediatric patients and the ability to metabolize PCT more slowly by pediatric population as compared to adult population, but this hypothesis needs to be further studied [15,16].

Our study provides an in-depth analysis of the effect of CPB on the kinetics of biomarkers after paediatric cardiac surgery. Firstly, we studied the trend of biomarkers till POD 5. Secondly, we conducted pair wise analysis of values on subsequent days. Thirdly, we evaluated the effect of CPB on peak values in addition to the values at each of subsequent alternate days till POD 5. Thus, we believe our study provides a more accurate analysis of the effect of CPB on kinetics of these biomarkers, which would help in establishing the current status of PCT in this subset of patients.

Conclusion

In conclusion, our findings show that paediatric cardiac surgery under CPB leads to increase in the levels of PCT, CRP and TLC above normal post-operatively in the absence of infection, during the first five PODs, thus limiting its diagnostic usefulness in early postoperative period at least during first five PODs.

Rapid kinetics of PCT appears to favour it relatively over CRP and TLC, as a diagnostic marker of infection postoperatively.

However, as the PCT levels are influenced by CPB during immediate postoperative period, hence a single elevated level in isolation cannot be considered to be indicator of infection. Only the maintenance of a high level and/or a delayed increase in PCT beyond

the early period could be used as an indicator of postoperative infection. Thus, following the trend of PCT is more important in this regard. Therefore, serial PCT measurements may have a role as a diagnostic marker of infection in post-operative period. However, considering the high cost for PCT measurements, serial testing of PCT may be of concern.

Peak PCT levels showed a positive correlation with the length of ICU stay whereas CRP or TLC levels do not show any correlation with the length of ICU stay. Hence, PCT may be better than CRP/TLC as a prognostic biomarker (prolonged ICU stay) in this population.

To summarize, although PCT appears to be influenced by CPB, but due to rapid kinetics, PCT may have following roles after paediatric cardiac surgery under CPB:

1. The role of PCT in diagnosing postoperative infection in the immediate post-surgical period is debatable due to the influence of CPB in pediatric cardiac surgery patients. Serial measures, showing persistently elevated levels or a second rise after an initial fall, may indicate infection. However, further research is needed as this study only included data up to 5 days post-operation.
2. PCT can help evaluate the response to treatment, with a rapid decrease in PCT levels indicating successful treatment, removal of infection triggers, or resolution of infection.
3. PCT may be useful in predicting postoperative outcomes, such as prolonged ICU stay.
4. Therefore, PCT may not be considered an ideal biomarker of post-operative infections in paediatric cardiac surgery under CPB, warranting continuous exploration till the last word is out.

Declarations

Ethical Clearance

The study approved by the Institutional Review Board at Postgraduate Institute of Medical Education & Research, Chandigarh, number NK/3984/M. Ch, dated 4/12/2017.

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None

Conflict of interest

None

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