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# C-Reactive Protein And Procalcitonin As Biomarker Of Sepsis After Congenital Heart Surgery

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***Abstract***

Introduction: Post pediatric cardiac surgery, blood infections remains the common cause of morbidity and mortality, therefore early detection of sepsis and treatment with appropriate antibiotics are mandatory to diagnose and treat infection earliest as well as to reduce the overall duration of ICU stay. After congenital heart surgery (CHS), Cardiopulmonary bypass (CPB), Delayed sternal closure and Low cardiac output due to ventricular dysfunction in immediate post operatively period can cause systemic inflammatory response syndrome (SIRS) which is difficult to differentiate from proven post operative infection.C – Reactive Protein (CRP) and Procalcitonin (PCT) has emerged as potential early biomarkers not only to diagnose sepsis but also guide the need for empirical antibiotic therapy and duration of antibiotics. However their utilities in differentiating between blood infection (BI) and SIRS in post operative period in various post operative days remains unclear. We aimed to determine optimal CRP and PCT level in post operative period for distinguish BI from SIRS. We also aimed to determine which biomarker is more sensitive and more accurate to diagnose infection effectively after congenital heart surgery.

Purpose: To study the trend and usefulness of CRP and PCT after CHS to diagnose infection in children below 6 months of age.

Material and Methods : In this Single-center retrospective observational study, medical records of 99 patients (65 male and 34 female) with age range of 0-6 months admitted in our center between January 2017 to July 2017 were reviewed. Children above 6 months of age and pre-operative culture proven infection were excluded. In PCICU, for each patient the following data were recorded : age, sex, date of admission, date of discharge, diagnosis, echo findings, any significant preoperative co-morbidity, infection, along with relevant surgical details including CPB time, Aortic cross clamp time, Total Circulatory Arrest Time, Number of days Sternum left open, Duration of mechanical ventilation, number of blood culture proven infection, post operative antibiotics usage and up-gradation of antibiotics, duration of ICU stay and patient's outcome were noted.

CRP and PCT levels were recorded preoperatively and on post-operative day (POD) 1, 3 & 5, along with other necessary investigations to diagnose infection. After assimilation of data, the infected and non-infected groups were compared with respect to trend of CRP and PCT level. Receiver operating characteristic (ROC) curve was used to arrive the cut off level of CRP, Procalcitonin(PCT).We have also studied the sensitivity of them along with their co-relation with duration of mechanical ventilation, CPB Time, open sternum cases and total days of PCICU stay.

Statical Analysis: Variables distribution was analyzed by the Kolmogorov-Smirnov test and Anderson-Darling test. For variables with normal distribution, we reported mean and standard deviation. Variables without a normal distribution were expressed as median and ranges. Normally distributed continuous variables were analyzed using the t-test. The Chi-square and Fisher's exact test was used for binary variables, and the Mann–Whitney U test was used for nonparametric variables. The diagnostic performance of PCT and CRP was evaluated using a receiver operating characteristic (ROC) curve. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software (Version 22). A value of P< 0.05 was used to determine statistical significance.

Table1: Clinical Characteristics of patients

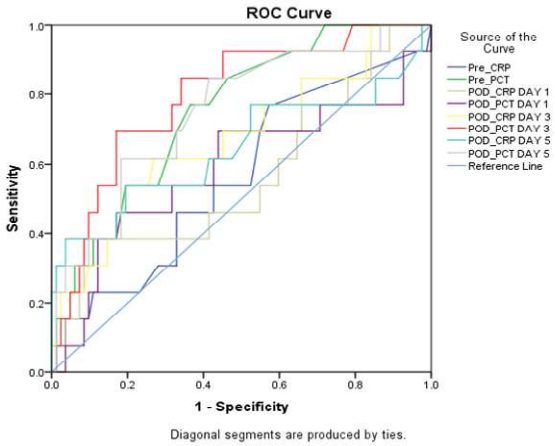
| Clinical Characteristics | All patients (n=99) | Infected (n=14) | Noninfected (n=85) | p-value* |
|---|---|---|---|---|
| Age (Days)$ | 75.65 ± 56.90 | 47.86 ± 45.23 | 80.22 ± 57.54 | **0.048** |
| Weight | 3.70 ± 1.03 | 3.30 ± 1.26 | 3.77 ± 0.98 | 0.11 |
| (Kilograms)$ | | | | |
| Gender | | | | |
| Male | 65 (66%) | 7 (50%) | 58 (68%) | |
| Female | 34 (34%) | 7 (50%) | 27 (32%) | |
| Chest | | | | |
| Yes | 31 (31%) | 7 (50%) | 24 (28%) | |
| No | 68 (69%) | 7 (50%) | 61 (72%) | |
| CPB Time (minutes)$ | 163.06 ± 92.07(n=90) | 169.83 ± 94.00(n=12) | 162.01 ± 92.34(n=78) | 0.78 |
| ACC Time (minutes)$ | 90.48 ± 56.58(n=88) | 89.82 ± 46.46(n=11) | 90.57 ±58.14(n=77) | 0.97 |
| TCA Time (minutes)$ | 63.42 ± 46.72(n=19) | 66.00 ± 15.28(n=5) | 62.50 ± 54.28(n=14) | 0.89 |
| CRP | | | | |

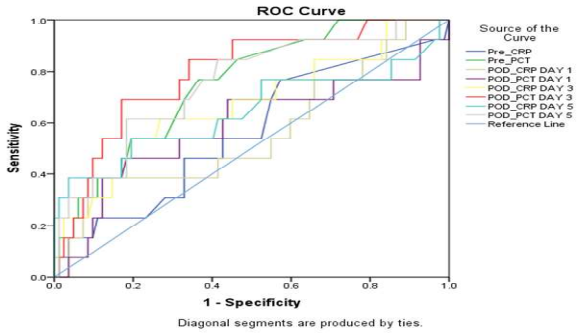
| | | | | |
|---|---|---|---|---|
| **Pre-operative$** | 0.61 ±1.32 | 1.15 ± 2.17 | 0.52 ± 1.11 | 0.09 |
| **POD1$** | 10.70 ± 4.93 | 11.63 ± 5.06 | 10.55 ± 4.92 | 0.45 |
| **POD3$** | 9.08 ± 5.00 | 11.96 ± 5.68 | 8.61 ± 4.76 | **0.02** |
| **POD5$** | 4.06 ± 3.51(n=95) | 7.02 ± 6.76(n=13) | 3.59 ± 2.43(n=82) | **0.001** |
| **PCT** | | | | |
| **Pre-operative#** | 0.11 (0.07-0.25) | 0.27 (0.13-3.87) | 0.10 (0.06-0.20) | **0.001** |
| **POD1#** | 7.98 (2.80-14.30) | 14.10 (2.61-30.58) | 6.30 (2.75-12.85) | 0.155 |
| **POD3$** | 6.86 ± 10.92(n=97) | 16.10 ± 14.83 | 5.31 ± 9.37(n=83) | **<0.001** |
| **POD5$** | 1.91 ± 4.04(n=95) | 5.19 ± 6.99(n=13) | 1.39 ± 3.12(n=82) | **0.001** |

Table2: ROC curve for CRP and PCT in patient's post-operative day.

| Day | CRP | PCT |
|---|---|---|
| Pre-operative | 0.56 | 0.75 |
| Day 1 | 0.56 | 0.59 |
| Day 3 | 0.67 | 0.79 |
| Day 5 | 0.64 | 0.75 |

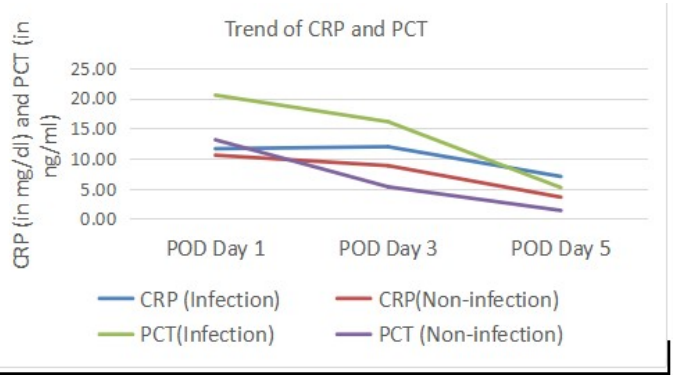
Kindly refer the attachment article table 3 below result for interpretation




Results:In our study, incidence of infection in younger children is significantly higher than older children; P= 0.048. Incidence of infection with open sternum (22.58%) were higher than that of closed sternum cases (10.29%). The median CRP for the Infected group on POD 3(11.96±5.68mg/dl) and POD 5 (7.02± 6.76mg/dl) were significantly higher than that of non-infected group POD 3; (8.61±4.76mg/dl & POD 5;(3.59±2.43mg/dl); P = 0.02 ; P=0.01. The median PCT for the Infected group on POD 3 (16.10 ±14.83 ng/ml) and POD5(5.19±6.99 ng/ml)were higher than that of non-infected group (POD 3; 5.31±9.37 ng/ml & POD 5; 1.39±3.12 ng/ml); P= <0.001, P=0.001.

The PCT level that yielded the best compromise between the sensitivity 92.5 % on POD3 with cut off 2ng/ml with an area under the ROC curve of 0.79 and 61.5% sensitivity on POD 5 with cut off 1ng/ml with area under the ROC curve of 0.75. Area beneath the ROC curve for CRP and PCT on POD 1, 3, 5 are 0.56, 0.67,0.64 and 0.59,0.79,0.75 respectively.




Discussion: The aim of the study was to determine if PCT and CRP could be utilized to distinguish between patients with or without infection or sepsis among children who suspected to have an infection or sepsis after CHS. We found that PCT values are higher in infection & its value start declining early once patients started on appropriate antibiotics. In general by using PCT after CHS, we can shorten the overall ICU stay and can treat sepsis earliest. We also noticed that CRP levels are

also high in infected patients comparing to non infected patients but it is less sensitive as comparison with PCT.Incidence of infection with open sternum (22.58%) were higher than that of closed sternum cases (10.29%). These findings were in accordance with those of several prior studies like Das s et al. McMaster et al. compared the median PCT on PODs 1-5 of patients with known infection to patients without fever or suspicion of infection after CHS. Median PCT levels were significantly higher in the sepsis and local infection groups as compared to the non-infected group. Additionaly According to McMaster et al. a high C-reactive protein level after cardiac surgery fail to predict occurrence of an infection, which underlines the need for a reliable prediction rule Which is not truly acceptable according to our study because in our study sensitivity of CRP is fairly high in infected patients comparing to non infected patients. Similarly, Garcia et al. monitored the PCT levels in infants and children with systemic inflammatory response syndrome on POD 1-3 following CHS. Significant differences were detected in the PCT values of the BI group versus the non-BI group in the tests performed on POD 2 and POD 3. PCT values on POD 1 were higher in the BI group than in the non-BI group without a statistically significant difference.

The secondary objective of this study was to determine if the utility of PCT varied in the early and late postoperative periods. Multiple studies have examined the kinetics of PCT in children following CHS. There is an increase in PCT postoperatively with a peak at 24-48 h with a return toward the baseline level by 72-96 h. These findings are were similar to those reported in adults after cardiac surgery. For this reason, it has been hypothesized that the utility of PCT in distinguishing BI from SIRS may be decreased in the early postoperative period.The findings of the current study support this hypothesis. We found that when early and late postoperative time periods were analyzed separately, the median PCT levels were statistically significantly different in the BI and non-infected groups only during the late postoperative period. In contrast, in a study by Seguela et al. among children suspected of having infection after CHS, median PCT level was significantly higher in the infected group before POD 3 but on or after POD 3, there was no significant difference between the infected and non-infected groups.

In contrast, other studies have shown that a subset of patients without BI will have a PCT level above 2 ng/mL even after POD 3. Consequently, proposed threshold levels for the identification of BI in prior studies have varied widely, and several authors have suggested using different threshold values for different days or time periods. In the current study, a PCT level of 2 ng/mL was found to be the optimal threshold value for discrimination of infection. Even at this threshold value, PCT is not highly sensitive or specific for infection. The negative predictive value, however, is high. Based on these data, we deduce that in pediatric patients suspected of having infection after CHS requiring CPB, the presence of a PCT level less than 2 ng/mL makes BI unlikely. Furthermore, we found that although there was a trend toward a higher PCT value in the BI group in the early postoperative period. We speculate that these findings may allow clinicians to decrease antibiotic administration to this subset of patients. The limitations of this study include its retrospective and observational nature. In addition, the number of infected patients included was small. This was particularly relevant in the early postoperative time period, which may have confounded the findings.

Conclusion: After the 'On Pump' CHS,CRP and Procalcitonin are useful biomarkers to diagnose infection. We also noticed Procalcitonin is more sensitive as compare to CRP and it shows early declines with appropriate usage of antibiotics. A PCT less than 2 ng/mL makes BI unlikely in children suspected of infection after CHS.

***Biography:***

Dr Dhaval Darji, has completed his study in Pediatrics in the year 2014 from the international recognized board, New Delhi (Diplomate National Board) . He has finished his fellowship in PICU from India's one of the largest children hospital (Wadia Children Hospital Mumbai ). After that he has been trained in pediatric cardiac ICU from one of the top Corporate hospital in Mumbai . He has special love for kids and has specific passion for management of pediatric opd patients as well as pediatric and neonatal critical patients. He has done multiple studies e.g. Neonatal hypoglycaemia and it's complication , Role CRP and Procalcitonin as biomarkers after congenital open heart surgery which were about to present in national as well as international journals.

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