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# Diagnostic Utility of a Rapid Immunochromatographic Test for Procalcitonin in Paediatric Infections

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## ABSTRACT

Procalcitonin (PCT) is an inflammatory marker that has been used as an indicator of severe bacterial infection. A rapid immunochromatographic test was used in this study, which can be used for on-site detection of PCT. A prospective study was done in the Department of Microbiology of a tertiary care hospital from March 2021 to February 2022. 227 patients were included in the study. Respiratory tract infection was the commonest infection (40.8%) in children followed by central nervous system, gastrointestinal tract and urinary tract infections. Out of 227 patients, 23patients had positive blood culture. E.coli was the predominant isolate followed by Pseudomonas and Klebsiella. Serum CRP was positive in 69 patients (30.4%) and procalcitonin was positive in 117 (51.5%) patients.

***Keywords:*** Procalcitonin, Paediatric infections, C-reactive protein

## INTRODUCTION

Fever is often the only symptom of an ongoing infection in infants and young children. Most often clinicians find it difficult to differentiate viral infections from bacterial infections.

Most bacterial infection can quickly escalate to a severe infection such as pneumonia and even sepsis. Morbidity and mortality in Pediatric intensive care units (PICU) are commonly related to severe infections and sepsis.[1] Therefore, pediatricians often choose to prescribe antibiotics despite the risk of antibiotic overuse and resistance.

To avoid unnecessary antibiotic use, diagnostic inflammatory markers that can suggest the occurrences of bacterial diseases quickly and accurately are required. Inflammatory markers which are widely used include white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), or C-reactive protein (CRP). Procalcitonin as a marker in bacterial infections has generated a lot of interest recently. In this study, a rapid immunochromatographic test was used for determination of procalcitonin levels in blood or serum in paediatric patients with infection.

## LITERATURE REVIEW

During bacterial infections, circulating phagocytes are activated and multiple mediators are released into blood. These cytokines, which are produced by macrophages, monocytes, and other cells participating in the inflammatory response, then stimulate production of acute phase reactants (APR) by the liver.[2] Important APRs include erythrocyte sedimentation rate (ESR), C- reactive protein (CRP), procalcitonin (PCT), serum amyloid A (SAA) protein, fibrinogen, ferritin, alpha-1 antitrypsin, haptoglobin, alpha-1 acid

glycoprotein, ceruloplasmin, and complement proteins C3 and C4.[3]

ESR and CRP are currently the most commonly used acute phase markers in clinical practice. ESR measures the rate at which red cells in a column of anticoagulated blood descends over a period of one hour. Any condition that affects red blood cells or fibrinogen levels alters the value of the ESR. Apart from infectious diseases, non-inflammatory conditions such as age, anaemia, pregnancy, drugs, and obesity can also cause an elevation in ESR.

C-reactive protein (CRP) is one of the earliest discovered biomarkers used to diagnose infection. C-reactive protein (CRP) was first discovered in 1930 in the serum of patients with acute Pneumococcal pneumonia.[4] CRP is primarily produced by the liver in response to cytokines, mainly IL-6 and its levels increase within 4–6 hours of an inflammatory stimulus.

Procalcitonin as a marker in infections has also generated a lot of interest. Studies have proved the role of Procalcitonin to differentiate bacterial infection from a viral or non-infectious inflammatory reaction. Other acute-phase markers are not used regularly for many reasons such as difficulty in measuring levels and lack of standardization.

Procalcitonin, normally produced in the C-cells of the thyroid gland, is the precursor of calcitonin. Procalcitonin (PCT) is a 116 amino acid protein with a sequence identical to that of the prohormone of calcitonin (32 amino acids). A specific protease cleaves procalcitonin to calcitonin, katacalcin, and an N-terminal residue. Normally, all procalcitonin is cleaved and none is released into the blood stream. Procalcitonin levels are therefore undetectable (<0.1ng/ml) in healthy humans. In systemic inflammatory conditions, in particular, bacterial infections, parenchymal cells produce large amounts of PCT, modulated by lipopolysaccharides and sepsis-related cytokines such as interleukin-1 and TNF-α.[5] During severe infections with systemic manifestations, procalcitonin levels may increase to over 100ng/ml.

Procalcitonin has several advantages over CRP and ESR as a biological marker. Serum concentrations of PCT are normally <0.05 ng/mL. As a cut-off for the diagnosis of sepsis, plasma levels of ≥0.5 ng/mL are interpreted as abnormal and suggest sepsis.[6] Procalcitonin levels become detectable rapidly, within 2–4 hours and peak within 6–24 hours, which is earlier than both CRP and ESR. ESR rises within 24–48 hours of the onset of inflammation, whereas CRP begins to rise after 12-24 hours and peaks within 2-3 days.[7]

An ideal marker for bacterial infections should allow not only an early diagnosis but should also give an idea about the course and prognosis of the disease. After successful treatment intervention, procalcitonin value decreases, indicating a positive prognosis.

The PCT molecule is very stable both in vivo and in vitro. Therefore no special requirements to pre-analytical sample handling and storage are required. Therefore, PCT can be considered superior to ESR and CRP as a biomarker in the diagnosis of bacterial infections.

The currently available methods for determination of procalcitonin, such as ELFA (Enzyme- linked fluorescent assay), luminometric immunoassay (ILA), Chemiluminescent immunoassay are automated platforms and are expensive.

## MATERIALS & METHODS

A prospective study was done in the Department of Microbiology of a tertiary care hospital from March 2021 to February 2022. All patients admitted in PICU or paediatric ward and whose blood samples were sent to Microbiology laboratory for CRP testing and blood culture were included in the study.

Based on the review of literature, the estimated sample size was 227 subjects.

CRP concentrations in serum were measured using latex agglutination test.

Blood culture was done using automated BacT/alert 3D Biomerieux system.

For immunochromatographic test for procalcitonin antigen, anti-procalcitonin antibody and Goat Anti-Mouse Colloidal Gold conjugate was coated on the test strip.

## RESULT

The total patients during the study period were 227. Seventy four were newborn babies.

**Table 1: Focus of infection of the children admitted**

| Site of infection | Percentage |
|---|---|
| Respiratory tract infections | 40.8% |
| Central nervous system infections | 10.4% |
| Gastrointestinal infections | 5.2% |
| Urinary tract infections | 5.2% |
| Covid | 7.8% |
| Babies born to Covid positive mothers | 6.9% |
| Other infections | 23.7% |

Blood samples were obtained from all the recruited patients for CRP and procalcitonin test. Samples for blood culture were obtained only from 64 patients. Isolates were obtained from 23 blood samples; twenty bacterial isolates and three yeasts.

**Table 2: Isolates from blood**

| Blood culture isolates | No: of patients | Percentage |
|---|---|---|
| Methicillin resistant Staphylococcus aureus (MRSA) | 1 | 4.3% |
| Salmonella typhi | 1 | 4.3% |
| Klebsiella species | 3 | 13.04% |
| E.coli | 4 | 17.39% |
| Pseudomonas aeruginosa | 3 | 13.04% |
| Burkholderiacepacia | 1 | 4.3% |
| Stenotrophomonas maltophila | 1 | 4.3% |
| Citrobacter species | 1 | 4.3% |
| Flavobacterium meningosepticum | 1 | 4.3% |
| Acinetobacter species | 2 | 8.6% |
| Aeromonas salmonicida | 1 | 4.3% |
| Beta lytic Streptococci | 1 | 4.3% |
| Candida albicans | 1 | 4.3% |
| Candida parapsilosis | 2 | 8.6% |
| No Growth | 41 | 64.06% |
| Total | 64 | 100% |

E.coli was the predominant isolate followed by Klebsiella species and Pseudomonas aeruginosa. Out of the four isolates of E.coli, two were multi-drug resistant (MDR) E.coli and out of the three isolates of Klebsiella, 2 were MDR Klebsiella and one was an ESBL (Extended spectrum β lactamase) Klebsiella.

**Table 3: C-reactive protein in patients with infection**

| CRP | No: of patients | Percentage |
|---|---|---|
| Negative | 158 | 69.6% |
| Positive | 69 | 30.4% |

**Table 4: Procalcitonin in patients with infection**

| PCT | No: of patients | Percentage |
|---|---|---|
| Negative | 110 | 48.5% |
| Positive | 117 | 51.5% |

C reactive protein was positive for 69 patients recruited and PCT for 117 patients. Six patients, who were CRP positive, were negative for PCT. All six patients were diagnosed with viral fever.

Twenty six patients who were PCT positive were negative for CRP. Eight among the twenty six patients presented with respiratory tract infections, one with urinary tract infection, four with febrile seizure, six with preterm sepsis and one with cellulitis. Four patients were Covid positive and two were babies born to Covid positive mothers.

Immunochromatographic test for procalcitonin showed a sensitivity of 70.6% and specificity of 72.9%.

## DISCUSSION

Timely diagnosis of systemic bacterial infection in children is the basis for effective treatment and control. A wide variety of acute-phase reactants have been evaluated as potential biomarkers for ruling out sepsis in paediatrics.

CRP has been the widely used biomarker for diagnosis of infection and inflammation.

However, CRP shows a delayed increase during an infection compared to PCT, resulting in false-negative results in the early stages of the disease. CRP can also be elevated in viral infections, limiting its ability to discriminate between bacterial and viral aetiologies.

In this study, procalcitonin (PCT) has been evaluated as a serum biomarker. A rapid immunochromatographic test has been developed to test for procalcitonin. In order to perform this test no sophisticated equipments are required unlike the other currently available methods for determination of PCT and hence it can be used as a point of care bedside test.

51.5% people in the study tested positive for PCT, but only 30.4% gave a positive CRP result. Literature suggests that PCT may provide a slight diagnostic advantage due in part to its rapid kinetic profile. PCT reaches peak serum concentrations at 6–12 hours following an infection, compared to 24–48 hours for CRP.[8] Since levels peak earlier, PCT can provide diagnostic information earlier during the course of infection, potentially before advanced clinical signs are apparent.

Pneumonia and acute respiratory infections (ARI) are the commonest infections affecting paediatric age group and is a major cause of morbidity and mortality. ARI can be caused by a heterogeneous group of both bacteria and viruses. Prompt antibiotic treatment is crucial for the effective management of bacterial ARIs. 40.8% of our patients presented with respiratory tract infections. 80.4% of the patients with respiratory infections were PCT positive and CRP was positive only in 34.78% patients.

Central nervous system infections were reported in 10.4% of the children studied. 90% of these children were PCT positive and only 40% showed a positive CRP. In an observational study by Alkholi *et al*, patients with bacterial meningitis were found to have increased serum PCT at the time of diagnosis. [9]

5.2% children suffered from gastrointestinal infections and 5.2% from urinary tract infections. PCT was positive in all the children reported with UTI whereas CRP was positive only in 33.3% cases. In a study conducted by Rui Ying Xu et al, PCT has higher sensitivity and specificity in predicting pyelonephritis than CRP.[10] All children with gastrointestinal infections had a positive PCT and CRP.

13 out of 227 patients were Covid positive and 10 babies were born to Covid positive mothers. 38.4% of Covid positive patients were PCT positive and 50% of babies born to Covid positive mothers were also PCT positive. Studies have shown that PCT may be an indicator of disease severity in COVID-19 and may contribute to determining the severity of patients infected with SARS-CoV-2.[11] Elevated procalcitonin levels are observed in infants born to mothers with COVID-19, which could indicate risk for neonatal sepsis.[12]

In newborns without bacterial infection, increased PCT level was significantly associated with lower gestational age and respiratory difficulty during the first week of life. Seventy four patients studied were newborns. [13]

## CONCLUSION

PCT is a good candidate as a useful biomarker in the clinic. Serum PCT levels will rise significantly above normal in patients with sepsis and other bacterial infections. A rapid, user-friendly, inexpensive method for PCT detection is very necessary to meet the widespread application in the clinic.

### *Declaration by Authors*

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