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Procalcitonin as a Biomarker in Intensive Care Unit Patients with Sepsis

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Abstract: ***Inflammatory response is one of the primary responses to a microbial invasion, which leads to the systemic illness which is referred to as sepsis[1]. Sepsis is a Systemic Inflammatory Response Syndrome (SIRS) that affect all organs. WBC, C-reactive protein C-Reactive Protein (CRP) and interleukin-1 (IL-1) are the conventional markers used for diagnosis of sepsis. Cytokines like Tumor Necrosis Factor (TNF), IL-1 and IL-6 are elevated during sepsis, but they do not possess sufficient sensitivity or specificity for the development of clinical markers[2]. Blood culture is considered as the gold standard for the confirmation of bacteremia which can isolate and identify the causative agent and subsequently test the antimicrobial sensitivity, but the delayed process of bacterial culture emphasizes the early diagnosis of sepsis[3]. Several studies mentioned the advantages of the precursor molecule of calcitonin, namely procalcitonin as a biomarker for sepsis. The serum Procalcitonin (PCT) level rises rapidly than CRP levels and peaks within very short time; moreover, if the patient responds appropriately to the treatment, the level of PCT returns to normal range faster than CRP which makes it a better biomarker for sepsis[4]***

Keywords: Procalcitonin, Sepsis, Intensive Care Unit, C- Reactive Protein, Interleukin

1. Introduction

During the course of evolution, our immune system has eventually developed to deal with infectious pathogen invasions by various host defense mechanisms all types of microbes like bacteria, virus, fungi and parasites can cause sepsis, but bacteria cause the most common pathogenic invasion[5]. During sepsis, the microorganisms invade to the blood stream and directly proliferate locally and release various virulent factors into the bloodstream. These products can stimulate the release of endogenous mediators of sepsis from endothelial cells, monocytes, macrophages neutrophils and plasma cell precursors[6]. Sepsis-related inflammatory response arises when the body attempts to neutralize pathogenic infection which in turn leads to the activation of various mechanisms with the immune cells to secrete inflammatory protein which in turn damage tissues and organs of the host[7]. Clinical symptoms of sepsis include tachycardia, tachypnea, fever, leukocytosis, etc. Usually, severe sepsis is accompanied with hypoperfusion or dysfunction of at least one organ. Sepsis associated with Multiple Organ Dysfunction Syndrome (MODS) or hypotension is known as septic shock[8]. PCT, the precursor of the hormone calcitonin, has been used as a biomarker to aid in diagnosis of bacterial infection or sepsis, as well as in differentiating bacterial pneumonia from viral pneumonia and Chronic Obstructive Pulmonary Disease (COPD) [9].

Diagnosis of sepsis is especially challenging as the clinical criteria for its diagnosis overlap with non-infective causes of systemic inflammation. Early diagnosis allows for timely therapeutic measures to be initiated, whilst delay leads to sepsis-related morbidity and mortality[10]. The emergence of antibiotic resistance, on the other hand, calls for a more stringent effort to reduce antibiotic overuse[11]. There is growing evidence for the use of PCT guided antibiotic therapy, both for initiation and for discontinuation of antibiotics. Clinical algorithms with specific PCT cut-offs in various clinical settings and patient populations are used as part of the antibiotic stewardship program. Most compelling evidence for PCT use is in adults with respiratory tract infections and in the critically ill, where Randomized Controlled Trials (RCT) have demonstrated the safety and efficacy of PCT guided antibiotic therapy. For other types of infections, the evidence for the use of PCT measurement is limited to observational studies, with its safety and benefit remaining undefined[12].

PCT is a 116-amino acid peptide with a molecular weight of 14.5 kDa. It consists of three sections; the amino terminus (57 amino acids), immature calcitonin (33 amino acids) and Calcitonin Carboxyl-terminus Peptide-1 (CCP-1) also known as katacalcin (21 amino acids). Its production is governed by the CALC-1 on chromosome 11. The product of this gene, prePCT, undergoes proteolytic cleavage producing PCT, which is further processed to the mature calcitonin molecule. Transcription and translation of CALC-1 gene is normally confined to the thyroid C-cells and, to a lesser extent other neuroendocrine cells. Production is, however, activated in all parenchymal tissues in response to bacterial infection, mediated by cytokines IL-6, TNF-α and interleukin-1β [13]. These other tissues lack the ability to cleave PCT to its mature form, calcitonin, leading to accumulation of PCT[14]. Conversely, PCT production is attenuated by interferon-γ primarily secreted in response to

viral infection.1[5.] This characteristic makes PCT a more specific marker for bacterial infections.

Serum PCT concentration in healthy individuals is typically <0.1 µg/L[16]. In the presence of bacterial infection, PCT increases, and the degree of rise correlates with the severity of the infection. Patients with localized infection have smaller increases of PCT in comparison to those with generalized sepsis, severe sepsis and septic shock. A declining concentration usually reflects resolution of disease. PCT is detectable 3 to 4 h following an infection, following the release of TNF-α at 90 minutes and IL-6 at 3 h. It peaks at 6 to 12 h and has a half-life of about 24 h. This favorable kinetic profile, and its specificity and sensitivity for bacterial infection make it suitable for diagnosis and disease progression monitoring.

Factors which may cause a raised PCT apart from a bacterial infection include recent major surgery, severe trauma, severe burns and prolonged cardiogenic shock[17]. However, in the absence of infection, these patients should have decreased PCT levels on subsequent measurements. Other infections which can activate the release of cytokines include fungal and malarial infections[18]. Patients on medications which stimulate cytokine release such as OKT3, antilymphocyte globulins, alemtuzumab, IL-2 and granulocyte transfusion will also have an elevated PCT level[19]. Dysregulated PCT production leading to a high PCT is seen in patients with paraneoplastic syndromes due to medullary thyroid and small cell lung carcinomas[20]

Newborns have been observed to have a baseline PCT that is higher than seen in adults. PCT increases further over the first 24 hour after birth and stays elevated during the first 2 days of life[21].

The goal of this research is to give an overview about the importance of procalcitonin as an ideal biomarker with a high diagnostic accuracy, for an early and rapid diagnosis of sepsis particularly in Intensive Care Unit (ICU) patients

2. Materials and Methods

Samples were taken from 31 patients who were admitted in intensive care units of hospital with suspected septic condition.30 control samples are also taken. Those who have cardiac disease history, pregnancy, above 80 years of age and with non-infective causes are excluded and the age above 18 are included 2ml of venous blood sample were collected by venipuncture from the subjects in plane tubes. Serum was separated by centrifugation and used for the estimation of procalcitonin.

For the detection of procalcitonin a two-step immunometric technique is used, which involves the reaction of procalcitonin present in the sample with a biotinylated anti-procalcitonin antibody (rat monoclonal anti-procalcitonin) bound to streptavidin coated on a microwell in the first step. Unbound materials are removed by washings. The second step involves the reaction of antigen-antibody complex with a Horseradish Peroxidase (HRP) labelled antibody conjugate (mouse monoclonal anti-procalcitonin). Unbound materials are removed by washing. The bound HRP conjugate is measured by a luminescent reaction. A reagent containing luminogenic substrate (a luminol derivativeand a peracid salt) and an electron transfer agent is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amountHRP conjugate bound is directly proportional to the concentration of procalcitonin present.

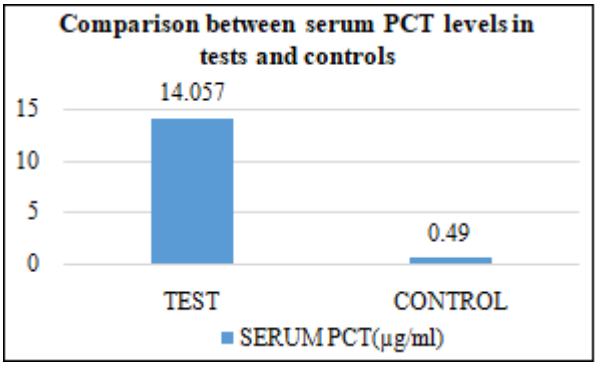
Sepsis identification is done with the help of BacT/Alert-an automatic microbial detection system based on the colorimetric detection of carbon dioxide produced by growing microorganisms

3. Observation and Result

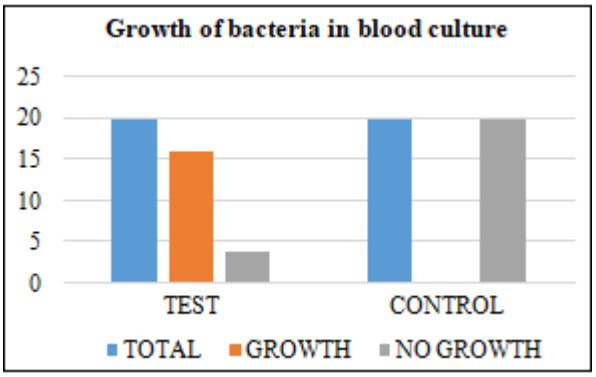
The total number of subjects included in this study was 61. Among these 31 were consider as tests and 30 were as controls.

Table: Distribution of cases and controls with respect to serum PCT level

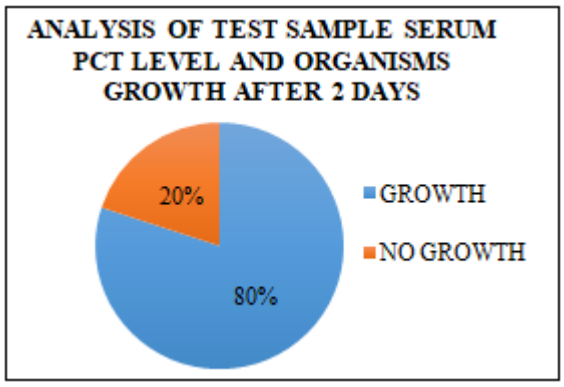
Normal value	Mean value (cases)	Mean value (controls)
0-2µg/mL >4µg/mL (Critical Range)	14.057µg/mL	0.490 µg/mL



Graph 1: Comparison between serum PCT levels in tests and controls (µg/ml).



Graph 2: Determination of growth of organisms in blood culture after 2 days.



Graph 3: Analysis of test serum PCT level and growth of organisms

As per Graph, 80% shows growth of organisms and their serum PCT levels are above 4µg/ml i. e., above critical level.20% shows no growth and their serum PCT level are between 2µg/ml and 4µg/ml. Septic condition i. e., presence of organism is significantly seen above the critical value.

4. Discussion

The present study shows serum PCT level is act as an effective biomarker in Intensive Care Unit patients with sepsis.

In another study by Kim et alhave analyzed the level of PCT in group of 300 febrile patients, where the largest number had localized infection (137), 58 patients had proven bacteremia, 90 patients had a temperature of non-infectious etiology, while in 15 cases cause of fever could not be determined. The authors have shown that the values of PCT were significantly higher in patients with bacteremia, compared to non-bacteremia patients (11.9 ± 25.1 vs 2.5 ± 14.7 ng / ml, p <0.001) with AUC 0.753 in relation to 0, 696. At the same time, the value of CRP showed no significant difference in these groups (p = 0.298). The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for the nine cut-off values of PCT showed the highest NPV (95.4%) for the cut-off level of PCT <0.4 ng / ml, which reliably excluded the diagnosis of bacteremia. The sensitivity and specificity for the PCT cut-off of 0.5 ng / ml were 74.2% and 70.1%.

In another prospective study of authors from Albania, the importance of the PCT, CRP and total leukocyte count are compared among 99 patients who on admission in Emergency Department (ED) and ICU had at least two of

the five symptoms of SIRS. According to the clinical findings and the available diagnostic procedures, without the results of the markers of inflammation, the examinees have been selected in a group with a high risk for sepsis (60 patients) and in a group with no suspicion of sepsis (39 patients). The mean PCT value for the first group was 11.128 ng / ml, compared to 0.272 ng / ml in the second group of patients. The sensitivity and specificity of the cut-off value of PCT of 0.5 ng / ml for differentiating SIRS and sepsis were 97.4% and 96.6%, while the value of PCT of 2 and > 2 showed 100% specificity in the confirmation of sepsis diagnosis. The authors assume that, because of the high sensitivity and specificity, PCT is a useful marker in their management of septic patients. They also proved significant correlation (p 0, 001) of high values of PCT with the severity of the disease, which was determined by APACH II or SOFA score.

Serum PCT has 94% sensitivity in the present study. Harbarth *et al*. reported a sensitivity of 97%.5[0] The present results confirm earlier findings that demonstrate serum PCT as among the most promising sepsis markers in critically ill patients, capable of complementing clinical signs and routine lab parameters suggestive of severe infection at the time of ICU admission.

Brunkhorst *et al*. reported from their study that serum PCT levels increase with the increasing severity of the inflammatory response to infection.

In present study we have taken 61 individuals out of these 30 were controls and 31 are our tests. Mean value of serum PCT in test and control sample are 14.057 µg/mL and 0.49µg/mL respectively, which indicate a high rise of serum PCT level in test samples. Sepsis or organism load is later confirmed by BACTEK SYSTEM after 2 days. Another finding is that the organism's growth is detected in patients with serum PCT level above critical level i. e., above 4 µg/ml.

5. Conclusion

Our study was to determine the ability of serum procalcitonin as a biomarker in intensive care unit patients with sepsis. In everyday clinical practice, 24 to 48 hours are usually required to obtain the blood culture results. As a results, the outcome may be worse and the length of the stay is longer. Thus, estimation of PCT is a rapid and reliable test to rule out septic conditions. Serum PCT concentration increases in patients with bacterial infections.

Our findings suggest that the increase in serum PCT level shows presence of organisms. PCT has been proved to be a superior biomarker or prognostic tool for determining sepsis especially in intensive care units. Plasma levels of PCT in healthy individuals are quite low (<2µg/ml). For diagnosis of sepsis, cut off level is above 4µg/ml and are interpreted as abnormal and suggest sepsis.

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