Asian Journal of Medical Research Review Article

Procalcitonin: A Novel Sepsis Biomarker

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Abstract

Sepsis is one of the leading causes of mortality in critically ill patients despite the use of broad spectrum antibiotics and fluid resuscitation therapies. Microbiological culture requires time and is not positive in fifty percent of sepsis patients. Biomarkers can play an important role in the diagnosis and prognosis of sepsis and thus reducing mortality rate. Various traditional markers are available for the diagnosis of bacterial infection but their results are often misleading. Procalcitonin has recently been proposed as a marker of bacterial infection. Its level increases in cases of sepsis, septic shock and in severe inflammatory reactions. Procalcitonin measurement has been claimed as a helpful marker in bacterial infection and sepsis. In this mini review we have tried to briefly describe the importance of procalcitonin as a sepsis marker.

Keywords: Sepsis, Procalcitonin , Diagnosis and Prognosis.

INTRODUCTION

Sepsis is a serious medical condition that is characterized by a whole–body inflammatory state (called a systemic inflammatory response syndrome or SIRS) and the presence of a known or suspected infection. The body may develop this inflammatory response by the immune system to microbes in the blood, urine, lungs, skin, or other tissues**.** The diagnosis of sepsis has always been difficult, particularly in the presence of other non infectious conditions that can generate an inflammatory response such as trauma, burn, and major surgery. During the last years, several variables have been examined as suitable markers of infection and sepsis, but none have become a well established standard. The traditional clinical signs of infection and the routine laboratory tests of sepsis are non specific and at times misleading. Widespread administration of antibiotics increases the risk of antibiotic resistance, drug toxicity and increased medical cost. Despite the use of new treatment regime and advancement in technology, the mortality in sepsis is still high, often because of delayed diagnosis and lack of proper treatment. Thus, there is an urgent need for a specific and sensitive marker of sepsis which would help in better management of patients with sepsis.

In 1993, Assicot et al described elevations in serum procalcitonin (PCT) as a marker of bacterial sepsis.[1] Since then it has been variously studied, examined and found to be a reliable indicator for sepsis.

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Biology of PCT

Procalcitonin was first identified from a medullary thyroid carcinoma cellline.[2] It is a 116 amino acid protein with a sequence identical to that of the prohormone of calcitonin.[3] Under normal conditions a specific protease cleaves all PCT to calcitonin, katacalcin and an N-terminal residue and hence in healthy individual PCT levels are either too low or undetectable. However, in severe bacterial infection and sepsis, intact PCT is found in the blood. In case of severe sepsis, concentrations of PCT may reach upto 1000 ng/mL.

In healthy persons, PCT is synthesized by the C cells of the thyroid. However, in microbial infection there can be alternate pathways. Muller et al in 2001 described that PCT synthesis can be induced by inflammatory cytokines like IL-1 â, TNF-á and also by lipopolysaccharides.[4] They could detect mRNA for PCT in all investigated tissues.

No specific route of elimination of PCT has yet been established. Probably it is degraded by proteolysis like other plasma proteins. Renal excretion plays a minor role.[5,6] Half life of PCT is about 20-24 hours.[7, 8] The tissue of origin of PCT in sepsis has not been confirmed, though there are studies that suggest activated macrophages and hepatocytes might be the possible site of origin.[9]

PCT induction is very rapid. A study conducted by Dandona et al,[8] has revealed that PCT synthesis can be stimulated by injecting small quantities of

Escherichia coli endotoxin in healthy individuals. Initially the level increases within 2-6 hours, reaching plateau after 6-12 hours. The concentration remains high for up to 48 hours, falling to baseline within the following 2days.

Function of PCT

Currently there is no explanation regarding the physiologic actions of PCT. Nylen et al in 1998,[10] revealed that high levels of PCT is toxic. In his experiment on sepsis induced hamster, the PCT levels were very high which increased mortality from 43% to 93% and after treatment with anti PCT antibodies, mortality decreased from 62% to 6%. The mechanism by which the toxicity occurs is still unknown and needs further investigation.

Diagnostic value of PCT

PCT has been found to have beneficial diagnostic value. Its measurement may be helpful in early diagnosis of infection in critically ill patients which could prevent further complications. The findings of many clinical studies have established the superior diagnostic accuracy of PCT in comparison to other parameters for the diagnosis of sepsis.[11- 13] It shows an initial increase upon infection and a more rapid decrease when the infection is controlled and hence can be used to guide antibiotic therapy. Studies have also shown that PCT correlates with the severity of sepsis. Initial data relating to a correlation between PCT and severity of sepsis was published by Zeniet al in 1994 [14] The optimal cut off values of PCT is variable and therefore clinicians should use the PCT result in conjunctionwith other laboratory findings and clinical signs of the patient. The reference range of PCT given in table 1 should be considered keeping the clinical aspect of the patient in mind.

PCT values are physiologically increased in neonates and the adult reference range applies three days after birth.[15] Raised PCT levels have been reported in malaria,[16, 17] but is not a specific diagnostic marker for the detection of plasmodia. In fungal and viral infections levels are occasionally elevated.

Prognostic value of PCT

Increasing or decreasing levels of PCT is crucial in confirming the diagnosis and therapeutic interventions. Its level reflects the extent of systemic inflammation secondary to infection. An initial high value of PCT level does not reflect poor prognosis. Specific treatment can be successful and prognostic evaluation based on changes in PCT levels should be preferred for assessment of individual values and initial peak value. Our preliminary study on forty patients has demonstrated that PCT levels declined significantly in patients who responded to treatment and also change in treatment instituted subsequent to consistently high PCT levels improved patients clinical response.[18] In localized infections the level of PCT is usually lower as compared to patients with systemic infections. PCT values quickly decline as the acute inflammation has waned, whereas the level does not return to normal in case of persistent systemic inflammation secondary to infection. Hence, increasing or persistently high PCT values indicate poor prognosis whereas declining values indicate a reducing inflammatory reaction, a favorable

Table1: Reference range of PCT

PCT < 0.5 ng/mL	Systemic infection is not likely. Local bacterial infection possible. If done very early should be reassessed 6-24 hours later.
PCT ≥ 0.5 and < 2 ng/mL	Systemic infection is possible. Patient should be closely monitored both clinically and by reassessing the PCT level within 6-24 hours.
PCT ≥ 2 and < 10 ng/mL	Systemic infection is likely. High risk for progression to severe systemic infection.
PCT ≥ 10 ng/mL	Systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock.

prognosis. Thus, serial estimation of PCT in patients with sepsis would help in assessing the severity of infection, the prognosis of disease and response to therapeutic measures which would eventually lead to better management of sepsis.

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