A Case Control Study of Procalcitonin as A Novel Bio Marker in Sepsis

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Abstract

Background: Sepsis is a leading cause of mortality in critically ill patients. Early diagnosis of sepsis followed by appropriate treatment decreases mortality and morbidity. The aim of this study is to assess the role of procalcitonin as a marker in the early diagnosis of sepsis.

Methods: A total of 50 patients with sepsis admitted to AMCU of seven hills hospital, Visakhapatnam from 1-11-2015 to 1-11-2016 were included in the study. Another 50 healthy persons with no clinical or biological data of infection, age and sex matched were included as a control group. Subjects were subjected to a thorough history taking and routine laboratory investigations. Serum procalcitonin was measured using Elecsys PCT assay on Roche Cobas e411 analyser. W.B.C was estimated by Sysmex xs -1000i Hematology Analyser.

Results: Mean levels of PCT and WBC in cases were significantly higher than in control groups, p<0.001. When compared PCT showed a direct positive correlation with WBC.

Conclusion: PCT alone or combined with WBC is a useful biomarker in early diagnosis of sepsis.

Keywords: Procalcitonin, Sepsis.

I. Introduction

Animals mount both local and systemic responses to microbes that traverse their epithelial barriers and enter underlying tissues. Fever or hypothermia, leukocytosis or lecopenia, tachypnea and tachycardia are the cardinal signs of systemic response that is often called as the systemic inflammatory response syndrome (SIRS). SIRS may have a infectious or a non infectious etiology. If a infection is suspected or proven a patient with SIRS is said to have sepsis. When sepsis is associated with dysfunction of organs distant from site of infection the patient has severe sepsis. Severe sepsis may be accompanied by hypotension or evidence of hypoperfusion. When hypotension cannot be corrected by infusing fluids the diagnosis is septic shock. (1) Sepsis is a potentially life threatening condition in which there is a widespread inflammatory state caused by the release of inflammatory mediators, including cytokines and kinins. These inflammatory mediators are released in response to infection and cause damage to the endothelium of blood vessels which allow them to leak fluid. This causes tissue edema, hypotension and hypoperfusion of organs. It also activates the clotting cascade, which leads to disseminated intravascular coagulation (DIC). The hypoperfusion of organs from hypotension or DIC may result in multiple organ failure and death.(2)

Procalcitonin is a 116 aminoacid peptide that has approximate molecular weight of 14.5 kda and belongs to the calcitonin (CT)super family of peptides.(3). Procalcitonin is encoded by calc -1 gene located on chromosome 11. Since the mid 1990’s there has been an increasing use of PCT measured in identifying sysmctic bacterial infections.(4) The short half life (25-30hours in plasma) of PCT, coupled with its virtual absence in health and specificity for bacterial infections gives it a clear advantage over the other markers of bacterial infections.(3,4).

II. Materials And Methods

This prospective case control study was conducted in seven hills hospital in visakhapatnam from 1-11-2015 to 1-11-2016. The study was approved by institutional ethical committee. The study sample included all patients aged above 18years presenting consecutively to our centre during the study period with acute sepsis, as diagnosed by one of the following: Clinical presentation of sepsis with positive blood culture, clinical presentation of urinary tract infection with positive urine culture, clinical presentation of pneumonia with supporting radiological features and positive sputum culture or other conditions with clinical and laboratory features compatible with sepsis.

Patients with history of malignancy, trauma or recent surgery were excluded from the study. Blood samples were drawn from all subjects within 24hrs of admission to the AMCU for complete blood count, procalcitonin, blood culture and other related tests. Serum PCT was measured using Elecsys PCT assay on Roche Cobas e411 analyser. The Elecsys PCT assay is a two step sandwich immunoassay with steptavidin
microparticles and an electro chemiluminiscence detection system. The test system reagents contain a biotinylated monoclonal PCT specific antibody and a ruthenium labeled monoclonal specific antibody. Total duration of assay -18 min. 1st incubation: Antigen in sample (30µl), a biotinylated monoclonal pct specific antibody labeled with a ruthenium complex react to form a sandwich complex. 2nd incubation: After addition of steptavidin coated microparticles the complex becomes bound to the solid phase via interaction of biotin and steptavidin.

The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with procell/procell. Application of a voltage to the electrode then induces chemiluminesccent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument specifically generated by a 2-point calibration and a master curve provided via the reagent barcode. The measuring range claim for the Elecys PCT assay is 0.02-100ng/ml. WBC count was estimated by Sysmex,xs-1000i Haematology Analyser. Estimation was done using fluorescence flow cytometry technology.

III. Statistical analysis

Statistical analysis was done using chi-square analysis and student ‘t’ test. p value <0.05 is significant

IV. Results

Overall 50 patients and 50 controls were included in the study. Figure 1 shows mean and SD of PCT in cases and controls. Figure 2 shows mean and SD of WBC in cases and controls. Figure 3 shows correlation of PCT with WBC in cases.

| Table No 1. Comparison of PCT Values in Cases & Controls: (n1=50, n2=50) |
|----------------------------------|-----------------|-----------------|
| 1) Parameters of PCT             | Cases(n=50)     | Controls(n=50)  |
| 1. Sample size (n)               | 50              | 50              |
| 2. Means                         | 51.36           | 0.03368         |
| 3. Standard deviation            | 32.45           | 0.007003        |
| 4. Mean difference               | 51.32           | 4.58            |
| 5. Standard Error                | 11.20           |                 |
| 6. Z - statistic                 |                 |                 |
| 7. P value                       | P < 0.001 ( Highly significant) |

II) Parameters of WBCs

| 1. Means                         | 24.70           | 7,508           |
| 2. Standard deviation            | 10,998.26       | 1152.60         |
| 3. Mean difference               | 16962.9         |                 |
| 4. Standard Error                | 1563.90         | 10.84           |
| 5. Z - statistic                 |                 |                 |
| 6. P value                       | P < 0.001 (Highly significant) |

III) Correlation between WBC & PCT Counts in Cases (n1=50, n2=50)

| 1. r - Value                      | 0.1578          | nearer to plus 1 is positive correlation. |
| 2. Significance test result       | t = 1.11 with 98 d.f ; P > 0.05 (Not significant ) |

IV) Correlation between WBC & PCT Counts in Controls (n1=50, n2=50)

| 1. r - Value                      | 0.9373          | nearer to plus 1 is positive correlation. |
| 2. Significance test result       | t = 18.51 with 98 d.f ; P < 0.001 (Highly significant) |

Fig – 1

COMPARISON OF MEANS & SD’S IN PCT CATEGORY OF CASES & CONTROLS
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Fig - 2

COMPARISON OF MEANS & SD’S IN WBC CATEGORY OF CASES & CONTROLS

Fig - 3

CORRELATION BETWEEN PCT & WBC COUNTS IN CASES
In the present study we have taken 50 cases with sepsis and 50 controls. The mean value of PCT in cases is 51.36 and controls is 0.3368. Standard deviation of PCT in cases is 32.45 and controls is 0.007. Standard error is 4.58. p value is <0.001 which is highly significant. Serum PCT levels have also been noted to increase with increasing severity of sepsis and organ dysfunction. This was demonstrated by Giamarellos-bourboulis et al. (5). This has led to interest in using PCT as a prognostic indicator in critical care patients and a number of studies have now been performed. One of the largest studies was performed by Jensen et al. (6). They found increase of PCT in sepsis and very high results correlated with high risk of mortality. Studies done by C.G. Chivate et al. showed statistically significant correlation of sepsis with increase in PCT values. (7)

The mean value of WBC in cases is 24.70 and controls is 7,508. p value is <0.001 which is highly significant. There is positive correlation between PCT and WBC in sepsis. Studies done by Magrini L et al showed PCT combined with WBC best diagnostic and prognostic power at ROC analysis in sepsis. (8)

Serum PCT, normally produced in the C-cells of the thyroid gland, is the precursor of calcitonin. A specific protease cleaves serum PCT to calcitonin, catacallin, and an N-terminal residue. Normally, all serum PCT is cleaved and none is released into the bloodstream. Serum PCT levels are therefore undetectable (<0.1 ng/ml) in healthy humans. During severe infections with systemic manifestations, however, serum PCT levels may increase to over 100 ng/ml. In these conditions, serum PCT is probably produced by extra-thyroid tissues. Patients who have previously undergone total thyroidectomy still produce high levels of serum PCT during severe infection. The exact origin of serum PCT during sepsis is uncertain.

The (patho) physiological role of serum PCT during sepsis is not clear. (9, 10) Serum PCT levels increase during severe generalized bacterial, parasitic or fungal infections with systemic manifestation. In severe viral infections, or inflammatory reactions of non-infectious origin, serum PCT levels do not increase or only show a moderate increase. Compared to the relatively short half-lives of cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, the half-life of serum PCT in the systemic circulation is 25-30 hours rather long. (11) Because of these properties, serum PCT has been proposed as an indicator of severe generalized infections or sepsis. (12, 13, 14)

Serum PCT is not a marker of infection as such since localized infections or infections with no systemic manifestation cause a limited, if any, increase in serum PCT levels. Although elevated serum PCT values during severe infections may decrease to very low levels with appropriate therapy, this does not always indicate complete eradication of the infection but only that generalization of the infection or the systemic response is under control. (15) Systemic inflammatory syndrome of non-infectious etiologies also leads to increases in serum PCT levels. Patients after major trauma or surgery and patients after cardiopulmonary bypass may present with increased serum PCT levels without any evidence of severe infection. However, the median values under these conditions are usually lesser than those found during severe sepsis and septic shock. (16)
VI. Conclusion

PCT alone or combined with WBC is a useful biomarker in early diagnosis of sepsis. Only procalcitonin improves accuracy of clinical sepsis diagnosis. PCT evaluation is a costly test but should be included in routine lab tests in sepsis patients for better patient outcome.

Conflict of interest: There is no conflict of interest to be declared.

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References