A STUDY OF SERUM PROCALCITONIN (PCT) AS A DIAGNOSTIC BIOMARKER IN SEPSIS IN ICU
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ABSTRACT

BACKGROUND
Sepsis is the most common cause of death in Intensive Care Unit (ICU) particularly in elderly, immunocompromised and critically ill patients. Definitive diagnosis of sepsis is positive blood culture and this takes long time to perform and being negative in many of the cases in order to assess the efficacy of the procalcitonin in diagnosing sepsis prospective study was conducted. Sepsis is diagnosed in early stage by measuring serum procalcitonin and value is correlated with the severity of sepsis.

MATERIALS AND METHODS
50 patients admitted in ICU diagnosed as sepsis were enrolled in the study. In addition to detailed history and physical examination, other necessary investigations including serum PCT level are done. Chi-square test was used to compare these variables. Procalcitonin values were analysed presented in terms of median.

RESULTS
Out of 50 patients, 28 were males and 22 were females. Diabetes is the most common comorbid condition associated with sepsis. Respiratory tract is the most common source of infection followed by UTI and cellulitis. As the severity of sepsis, increased number of death also increased and 100% of patients with septic shock had positive PCT value compared to 55% of patients with sepsis.

CONCLUSION
Sepsis is most common cause of morbidity and mortality in ICU. Even though, culture is considered as one of most important investigation, the sensitivity is less and time consuming. So, serum PCT is one of the diagnostic marker, which can be used for early diagnosis of sepsis and start empirical antibiotics thus reducing the mortality.

KEYWORDS
Procalcitonin, Sepsis, ICU.

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BACKGROUND
Sepsis is a leading contributory factor for death especially in noncoronary Intensive Care Unit (ICU). The incidence of severe sepsis and septic shock has increased over the past 30 years and the annual number of cases is now >7,50,000 (~3 per 1000 population).

Sepsis-related incidence and mortality rates increase with age and preexisting comorbidity. Early diagnosis of bacterial infection is of primary importance because early institution of an appropriate antimicrobial regimen after accurate diagnosis in infected patients is associated with a better outcome. In fact, blood cultures yield bacteria or fungi in only ~20-40% of cases of severe sepsis and 40-70% of cases of septic shock.

The established biological markers of inflammation (leucocytes, CRP (C-Reactive Protein))³ may often be influenced by parameters other than infection and may only be slowly released during progression of an infection. Since these common clinical and lab measurements lack sensitivity and specificity, other tests are needed to give an early marker of the infectious cause of a generalised inflammatory response to allow early diagnosis and for the use of specific treatment.

Procalcitonin (PCT) has emerged as the most studied and promising sepsis biomarker. For diagnostic and prognostic purposes in critical care, PCT is an advance on C-reactive protein and other traditional markers of sepsis.

Procalcitonin- Synthesis and Structure
Procalcitonin (PCT) is the precursor of calcitonin. Site of formation is the CALC-1 gene on chromosome 11 of the human genome. After translation from CT-DNA into mRNA, the first translation product is preprocalditonin, which then changes by different modification steps into PCT. PCT is a
peptide consisting of 116 amino acids. PCT is enzymatically degraded into lower molecular weight peptides. The final product consists of 32 amino acids and is named calcitonin. All precursors including PCT and the mature hormone peptide can be detected in serum of healthy humans. In septic patients, only the 3-116 fragment is detectable, not the complete PCT molecule.  

Neuroendocrine Pathway

Site of synthesis for PCT in healthy persons are the C-cells of the thyroid. Expression of CT-mRNA takes place only in the neuroendocrine cells. Release occurs in the form of the posttranslational processed hormone calcitonin enclosed in Golgi vesicles. This hormone plays an important role in the pathway and regulation of calcium and phosphate in the bone metabolism. 

Functions of Procalcitonin

Currently, there is no evidenced explanation concerning the function of PCT, only speculations. In 1998, Nylen et al. showed that high levels of PCT increased in experimental-induced sepsis in hamster (group 1), the mortality from 43% to 93%. After treatment with anti-PCT antibodies (group 2), the mortality decreased from 62% to 6%. Possibly PCT has the same effect as jasmine acid in plants, a hormone for apoptosis (Parthier 1991). It is possible that PCT plays not only a role in signal transduction as biomarker, but additionally an important biological role in the septic processes. This function needs still to be clarified. 

Procalcitonin Assay

PCT becomes detectable within 2 to 4 hours after a triggering event and peaks by 12 to 24 hours. PCT secretion parallels closely the severity of the inflammatory insult with higher levels associated with more severe disease and declining levels with resolution of illness. In the absence of an ongoing stimulus, PCT is eliminated with a half-life of 24 to 35 hours. PCT measured using a quantitative homogenous assay (BRAHMS, Hennigsdorf, Germany). The assay is based on Time-Resolved Amplified Cryptate Emission (TRACE) technology. A nitrogen laser at 337 nm is directed at a sample containing PCT and 2 fluorescently labeled antibodies recognizing different epitopes of the PCT peptide. The principal of the assay is based on the transfer of non-radiative energy between "donor" and "acceptor" molecules. The donor molecule upon excitation emits a long-lived fluorescent signal in the millisecond range at 620 nm, while the acceptor molecule upon excitation emits a short-lived signal in the nanosecond range at 665 nm. When both molecules are brought into close proximity by binding to PCT, the resultant signal is amplified at 665 nm and prolonged to last for a few microseconds. This prolongation ensures the signal can be measured after the background fluorescence (common in biological samples) has decayed. In the BRAHMS assay, the donor molecule is a Europium cryptates labeled polyclonal sheep antibody recognizing epitopes in the immature CT region, while the acceptor molecule is an XL665 labeled monoclonal antibody raised against the CCP-1 region of PCT. Samples suitable for the assay can be serum or plasma collected using either EDTA or heparin as the anticoagulants.

Measuring Range

The BRAHMS PCT KRYPTOR assay measures concentrations between 0.02 to 50 ng/mL directly and up to 5000 ng/mL after sample dilution. 

Limitations

PCT levels maybe elevated in patients who do not have sepsis. Plasma levels in these cases usually are not very high (<2 ng/mL), but they may increase significantly in certain conditions. 

- Severe trauma.
- Major burns.
- Multiorgan failure.
- Major surgery.
- Patients with history of malignancy.
- Patients who have undergone recent transplantation surgery.
- Patient who are on immunosuppressant treatment.

MATERIALS AND METHODS

This is a cross-sectional study included 50 consecutive patients aged above 18 yrs. who are diagnosed as sepsis based on American College of Chest Physician Guidelines and admitted to medical intensive care unit in Basaveshwara Teaching and General Hospital attached to Mahadevappa Rampure Medical College from November 2014 to May 2016. Patients with history of malignancy who have undergone recent transplantation surgery, patient who are on immunosuppressant treatment, trauma, burns excluded from the study and informed consent was taken from the included patients. 

Demographic data, history, clinical examinations and details of investigations has been recorded in the study proforma, which includes complete blood count with erythrocyte sedimentation rate, serum procalcitonin, urine routine and microscopy, chest x-ray, peripheral smear/ROT for malarial parasite and IgM culture/urine culture/sputum culture, chest x-ray, peripheral smear/ROT for malarial parasite, IgM-Leptospira and dengue check, arterial blood gas analysis, renal function tests, blood culture/urine culture/sputum culture, chest x-ray, peripheral smear/ROT for malarial parasite, IgM-Leptospira and dengue check, arterial blood gas analysis when indicated.

Data were analysed P value <0.05 was considered as statistically significant. Descriptive statistics of variables such as age, sex, groups of sepsis, etc. were analysed. Chi-square test was used to compare these variables. Procalcitonin values were analysed presented in terms of median since data was not normally distributed. Kruskal Wallis test was used to compare median procalcitonin between three groups. Mann-Whitney U test was used where two variables are present.
RESULTS AND DISCUSSION

Out of 50 patients enrolled in the study age, distribution is as follows (Table 1). Most common age group affected are between 18-35 yrs. This probably infers the occurrence of sepsis mostly in the younger age group.

In another study by Meynaar IA,14 mean age of patients with sepsis was 65 and those with SIRS was 62 years.

Sex Distribution

In this study, 28 patients (56%) were males and 22 patients (44%) were females (Figure 1). This is probably due to the increased prevalence of comorbid illnesses like diabetes mellitus in male patients in our study.

In a study by Sinha M et al,15 male were more with male-female ratio of 28:12, which is almost similar to the result of our study.

Comorbidities in the Study-

(Table 3) In this study, 36 of them had associated comorbid conditions. In that 36 patients, the most prevalent comorbid condition is diabetes mellitus 39.2% in males and females 22.7% followed by HTN in 25% of males and 4.5% females. Study done by Lai et al had 38% of population with diabetics.16

SIRS in Study Group

Tachycardia was the most common manifestation found in 47 patients (Table 4), followed by leucocytosis or leucopenia, which was found in 41 patients. Further, it was noticed that in the patients with septic shock leucocytosis/leucopenia was the most common manifestation found to be present in 100% of the patients. In contrast to studies done by Lai at al, Stucker et al who did not have tachypnoea as the common manifestation of SIRS.16,17

Type of Sepsis and Diagnostic Value of Serum PCT in the Study

Based on the ACCP definition guidelines, patients were classified as sepsis, severe sepsis and septic shock (Table 5). Accordingly, out of 50 patients, 27 (54%) were in the group of sepsis, 17 patients (34%) were in the group of severe sepsis and 6 patients (12%) were in the group of septic shock. Out of 33 patients who had a positive procalcitonin level of more than 0.5 ng/mL with the p value being 0.004, this correlated statistically with the presence of sepsis. Further, it correlated best in the groups with more severe forms of sepsis. All 6 patients (100%) (Table 6) in the group of septic shock had a positive procalcitonin level, whereas only 15 of 27 patients in the group of sepsis and 12 of 17 patients in the group of severe sepsis had positive procalcitonin. Out of 50 patients, 17 patients had a negative procalcitonin level of less than 0.5 ng/mL.

PCT Levels Co-Relation and Outcome in the Study Population

In our study, mean value of serum procalcitonin in the 54% patients with sepsis was 0.55 ng/mL, 8.15 ng/mL in 34% patients with severe sepsis and in the 12% patients with septic shock, it was 16.15 ng/mL. Thus, inferring that higher mean levels of serum procalcitonin were noticed in the groups with more severe sepsis (Table 7). Thus, quantitative correlation of higher values of serum procalcitonin with worse prognosis was established. As the severity of the sepsis increased, the death also increased from 11.1% in sepsis to 83.3% in septic shock (Table 8).

In the study by Sudhir U et al,18 26.9% of patients in the group of sepsis, 40% in the group of severe sepsis and 47.8% of patients in the group of septic shock had high serum procalcitonin levels of more than 10 ng/mL. This is similar to the results obtained in our study. This was comparable to various studies done previously Meisner et al, Stucker et al.19,17

There was significant association between the outcome and severity of sepsis with the p value being less than 0.05.

PCT Correlation with Outcome

In this study, median serum procalcitonin levels in the 9 patients who did not survive at the end of the study was 13.47 ng/mL (Table 9), whereas that in survivors was 4.58 ng/mL and the difference between the two groups was statistically very significant with the p value of 0.006.

PCT Correlation with Microbiological Result (Table 10)

Out of 50 patients, 8 (16%) patients had culture positive sepsis. Out of 8 patients, 4 had positive serum procalcitonin level, whereas 28 (71%) of 39 patients who had culture-negative sepsis had positive serum procalcitonin level.

This could be probably due to the lesser sample size of culture-positive patients as compared to the culture-negative patients for a statistically-appropriate calculation. Further, it can imply that serum procalcitonin can be used as a complementary diagnostic modality in the diagnosis of sepsis in addition to its utility in the prognosis of sepsis by quantitative correlation.

Focus of Sepsis

In our study, the most common focus of sepsis was respiratory tract (32%) (Table 11) followed by urinary tract (22%) and cellulitis (22%). Respiratory sepsis included lobar and bronchopneumonia, acute exacerbation of COPD secondary to infection, aspiration pneumonia and some of the patients developed ARDS as a complication of sepsis. Higher incidence of urinary tract infections probably due to the higher incidence of diabetes mellitus in our study.

This is similar to the study by Greg S Martin, which has shown that respiratory infections are the most common source of sepsis.20

<table>
<thead>
<tr>
<th>Age Group in Years</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-30</td>
<td>19</td>
<td>38</td>
</tr>
<tr>
<td>31-45</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>46-60</td>
<td>09</td>
<td>18</td>
</tr>
<tr>
<td>61-80</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1. Age Distribution
Sex | Number | Percentage
--- | --- | ---
Male | 28 | 56
Female | 22 | 44
Total | 50 | 100

**Table 2. Sex Distribution**

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Males Number (Out of 28) %</th>
<th>Females Number (Out of 22) %</th>
<th>Total</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>7 (25)</td>
<td>1 (4.5)</td>
<td>8</td>
<td>16.0</td>
</tr>
<tr>
<td>DM</td>
<td>11 (39.2)</td>
<td>5 (22.7)</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>BA/COPD</td>
<td>1 (3.5)</td>
<td>2 (9)</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>IHD</td>
<td>2 (7.14)</td>
<td>0 (0)</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>CVA</td>
<td>1 (3.5)</td>
<td>1 (4.5)</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>0 (0)</td>
<td>1 (4.5)</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>CLD</td>
<td>3 (10.7)</td>
<td>0 (0)</td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td>CKD</td>
<td>1 (3.5)</td>
<td>0 (0)</td>
<td>1</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Table 3. Comorbidities in Study Population**

HTN = Hypertension, DM = Diabetes mellitus, BA = Bronchial asthma, COPD = Chronic obstructive pulmonary disease, CVA = Cerebrovascular accident, CLD = Chronic liver disease, CKD = Chronic kidney disease.

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia (&gt;90b/min.)</td>
<td>26</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Tachypnoea (&gt;24/min.)</td>
<td>16</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>TLC (&gt;12000 and &lt;4000)</td>
<td>22</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Temp (&gt;38 D)</td>
<td>08</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Table 4. SIRS in Study Group**

SIRS = Systemic inflammatory response syndrome, TLC = Total leucocyte count.

<table>
<thead>
<tr>
<th>Types of Sepsis</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>17</td>
<td>34</td>
</tr>
<tr>
<td>Septic shock</td>
<td>06</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 5. Type of Sepsis**

<table>
<thead>
<tr>
<th>PCT</th>
<th>Sepsis</th>
<th>Severe Sepsis</th>
<th>Septic Shock</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (&lt;0.5 ng/mL)</td>
<td>12</td>
<td>05</td>
<td>0</td>
<td>27</td>
<td>0.004</td>
</tr>
<tr>
<td>Positive (≥0.5 ng/mL)</td>
<td>15</td>
<td>12</td>
<td>6</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>17</td>
<td>6</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6. Diagnostic Value of Serum PCT in the Study**

PCT = Procalcitonin

**Table 7. PCT Levels Co-Relation with Severity of Sepsis**

*Significant association between serum PCT levels and study group. P value <0.05.

With increase in severity of sepsis, levels of procalcitonin also increased.

<table>
<thead>
<tr>
<th>Types of Sepsis</th>
<th>Death</th>
<th>Survived</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>03 (11%)</td>
<td>24 (88.8%)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>04 (23%)</td>
<td>13 (76%)</td>
<td>17</td>
<td>0.001</td>
</tr>
<tr>
<td>Septic shock</td>
<td>05 (83.3%)</td>
<td>01 (16%)</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Table 8. Outcome in Study Population**

Significant association between outcome and study population p value = <0.05.

<table>
<thead>
<tr>
<th>Death</th>
<th>Survivor</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (Median)</td>
<td>13.47</td>
<td>4.58</td>
</tr>
</tbody>
</table>

**Table 9. PCT Correlation with Outcome**

<table>
<thead>
<tr>
<th>Culture +ve</th>
<th>Culture -ve</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCT (+ve)</td>
<td>04</td>
<td>28</td>
</tr>
<tr>
<td>PCT (-ve)</td>
<td>04</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>08</td>
<td>39</td>
</tr>
</tbody>
</table>

**Table 10. PCT Correlation with Microbiological Result**
CONCLUSION

Sepsis is one of the most common cause of admissions to ICU and emergency wards in most of the tertiary care centre with a significant mortality and morbidity. It results in financial burden to the society with arrays of investigations. Cultures for the infecting organism take a lead among all the investigations, even though it is specific, sometimes it is less sensitive. Thus, there is requirement of a cost-effective biomarker for early identification and aggressive treatment of patients with sepsis.

Serum procalcitonin done at the time of admission was proven to be the cost-effective biomarker for the early identification of sepsis and it is also found better than culture from our study. Along with the identification of sepsis, it can also be used as a simple prognostic marker when quantitatively estimated. This would warrant early initiation of effective treatment strategies. Thus, estimation of serum procalcitonin for diagnosis and prognostication of sepsis should be practiced.

REFERENCES


