Bacteremia in PD patients: Role of PCT

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Abstract:

The aim of this study is to analyze the usefulness of serum Procalcitonin levels as both diagnostic and prognostic marker for aerobic and anaerobic bacteremia and to assess the correlation between serum Procalcitonin and time to positivity. Retrospectively analyzed 410 Peritoneal Dialysis patients with suspected blood stream infections who had concurrent serum Procalcitonin data and blood culture results. The study illustrates that Procalcitonin assay is a reliable and promising biomarker to discriminate aerobic and anaerobic bacteremia from non-bacterial blood stream infections. Serum Procalcitonin levels may also predict the severity and prognosis of blood stream infections but renal function should also be taken into account.

Keywords: Peritoneal dialysis, Procalcitonin, Aerobe, Anaerobe, Bacteremia, ESRD.

Introduction

Patients with end-stage renal disease (ESRD) are more susceptible to systemic bacterial infections with worse outcome. Due to their compromised immune status, clinical signs for infection in these patients are often subtle and nonspecific and the conventional laboratory markers are often influenced by uremia (1). Furthermore, patients on chronic Peritoneal Dialysis (PD) therapy may have chronic systemic inflammation stimulated by an incompatibility of the biomaterial of the dialysis procedures (2,3). Therefore, it is difficult to differentiate between infectious causes and non-infectious causes of systemic inflammatory responses that are common among these patients.

Bacteremia and sepsis are potentially life-threatening and thus require early diagnosis and prompt administration of antibiotics to reduce mortality related to multiple organ failure (4,5). Blood cultures (BCs) are the “gold standard” for diagnosis of sepsis (6). However, test results are typically not available for the next 24 to 48 hours. This delay has prompted the use of a rapid and a reliable test to confirm or exclude the existence of blood-stream infection.

Procalcitonin (PCT), a 116-amino acid precursor protein of calcitonin, has been shown to be able to accurately distinguish bacterial from nonbacterial infections, or other sterile inflammation condition (7-9). PCT is constitutively produced in the C cells of the thyroid gland without hormone activity. It is rapidly produced and released to peripheral circulation in response to endotoxin and pro-inflammatory cytokines, such as IL-1β and TNF-α. Unlike CRP, PCT production is inhibited by interferon-gamma (IFN-γ), a cytokine that is produced during viral infection (10-16). PCT has not been extensively studied in PD patients and it was never analyzed with anaerobic bacteremia. Thus the aim of this study is to analyze...
the usefulness of PCT as both diagnostic and prognostic marker for aerobic and anaerobic bacteremia and to assess the correlation between PCT and time to detection in PD patients.

**Material and Methods**

We retrospectively analyzed the data of 410 PD patients with suspected bloodstream infections who had concurrent serum PCT data and blood culture results and were admitted from Jan 2000 to Mar 2016 at our centre. For each patient age, sex, underlying disease, Serum PCT levels, time of blood culture positivity, results of blood culture and its outcome were recorded.

Blood for Serum PCT and for blood culture was drawn simultaneously. Out of 15 ml of blood, 5 ml was kept for S. PCT while 5 ml blood was inoculated in FA bottle for the isolation of aeroobe and fungus and the remaining 5 ml in FN bottle for isolation of anaerobes. These two inoculated bottles were further incubated in BactAlert 3D system until a positive result was obtained else they would be kept up to 7 days according to protocol. Time till positivity was recorded and 0.5 ml blood was drawn from the positive bottles immediately and inoculated onto sheep blood agar, chocolate agar, MacConkey agar, anaerobic agar and Sabourauds agar at 37°C. Microorganisms were further identified by the Vitek-2 system (BioMerieux, France).

Serum PCT levels were measured in 200 µl sera according to the manufacturer's instructions via automatic analyser VIDAS B.R.A.H.M.S. (BioMerieux, France). The lower limit of detection of the assay was 0.05 ng/mL.

To assess the diagnostic value of PCT for bacteremia, blood cultures were classified into two groups- positive blood culture and negative blood culture. Positive blood cultures were further divided into three categories according to the microorganisms identified: Aerobes, Anaerobes and Fungi for the purpose of determining the usefulness of PCT for early diagnosis of bacteremia. Time to positivity (TTP) was defined as the interval between the start of incubation and detection of growth by the automated blood culture system.

Survival analysis was done to estimate the prognosis of survival of patients with Positive bloodstream infection. The date on which the blood culture was obtained and the follow-up information for a period of at least 30 days was compiled for all the patients. If a patient had more than one positive blood culture within the 30 days, only the first one was considered for survival analysis.

Data were expressed as mean + standard deviation. Statistical analysis was performed using chi square test, contingency coefficient and one-way ANOVA while significance was defined at p value of 0.05. Diagnostic accuracy was assessed by calculating the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver operating characteristic (ROC) curves were drawn and area under curve (AUC) was calculated to assess the diagnostic value of PCT, to discriminate bacteremia from fungemia and nonbacteremia. The correlation between PCT and TTP was assessed with the Spearman rank test and Kaplan-Meier method was used to estimate survival curves.

**Results**

Blood samples of 410 PD patients for PCT and blood cultures were taken simultaneously. Their base line and demographic data were described as follows. Out of 410 PD patients males were 63.9% and females were 36.1%, the mean age of the study population was 42.40 + 14.90 and predominant causes of ESRD in this group were (46.6%) diabetic nephropathy, (33.9%) glomerulonephritis, (17.3%) hypertension and (2.2%) unknown. Demographic features and blood culture results are described in Table 1.
Table 1: Demographic features and blood culture results

Demographic Features:
- Age: 42.40 ± 14.90
- Gender: Male 262 (63.9%), Female 148 (36.1%)

Primary Diagnosis:
- Diabetes: 191 (46.6%)
- Glomerulonephritis: 139 (33.9%)
- Hypertension: 71 (17.3%)
- Unknown: 9 (2.2%)

Results of Blood Culture:
- Total blood cultures: 410
- Positive blood cultures: 259 (63.2%)
- Aerobes isolated: 147 (56.9%)
- Anaerobes isolated: 76 (29.3%)
- Fungus isolated: 36 (13.8%)
- Negative blood cultures: 151 (36.8%)

Out of 410 blood samples, 63.2% samples were found positive and remaining 36.8% samples did not show any growth until 7th day, hence considered as negative. For these positive blood cultures, PCT levels were significantly correlated with TTP at 0.05 levels as depicted in Table 2.

Table 2: Correlation analysis between PCT and TTP of blood cultures

<table>
<thead>
<tr>
<th></th>
<th>Spearman's rho</th>
<th>Time of Detection HR</th>
<th>Serum PCT</th>
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<tbody>
<tr>
<td>Time of Detection Hr</td>
<td>Correlation coefficient</td>
<td>1.000</td>
<td>0.138*</td>
</tr>
<tr>
<td>Sig. (1-tailed)</td>
<td>0.0</td>
<td></td>
<td>0.049</td>
</tr>
<tr>
<td>N</td>
<td>259</td>
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<td>259</td>
</tr>
<tr>
<td>Serum PCT</td>
<td>Correlation coefficient</td>
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<td>Sig. (1-tailed)</td>
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<td>0.0</td>
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<tr>
<td>N</td>
<td>259</td>
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<td>259</td>
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</tbody>
</table>

Figure 1: (A) Spectrum of aerobes in Blood (B) ROC of aerobes (C) Area under curve for aerobes.

AUC Figure 1(C) in this ROC plot is 0.920 and the optimal cut off value of PCT for predicting aerobic blood stream infection was 1.3 ng/ml. Using this cut off value the sensitivity, the specificity, PPV and NPV were 90.0%, 70.3%, 55.1% and 94.5% respectively. Hence AUC signifies that PCT can accurately predict the aerobic blood stream infection and proved to be highly sensitive.
AUC Figure 2(C) in this ROC plot is 0.913 and the optimal cut off value of PCT for predicting anaerobic blood stream infection was 1.29 ng/ml. Using this cut off value the sensitivity, the specificity, PPV and NPV were 89.0%, 67.1%, 58.2% and 95.9% respectively. Hence AUC signifies that PCT can accurately predict the anaerobic blood stream infection and proved to be highly sensitive.

AUC Figure 3(C) in this ROC plot is 0.110 which illustrates that PCT is not useful to detect fungal blood stream infection.

AUC Figure 4(B) in this ROC plot is 0.016 which illustrates that PCT is not useful for Negative blood culture that means there is no blood stream infection.

Analysis between the PCT and the pathogens was done by the One Way ANOVA as depicted in Table 3 and the results suggested that after comparing means two subsets were found. Sterile blood culture and fungal blood culture formed one subset while aerobic and anaerobic blood stream infections formed the other subset. Hence, ANOVA analysis also indicates that PCT levels discriminate bacteremia from nonbacteremia and fungimia.
Table 3 One-way ANOVA analysis to compare means for groups in homogeneous subsets

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>Subset for alpha = 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>151</td>
<td>1</td>
</tr>
<tr>
<td>Fungus</td>
<td>36</td>
<td>0.6161</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>76</td>
<td>--</td>
</tr>
<tr>
<td>Aerobes</td>
<td>147</td>
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</tbody>
</table>

Our results also demonstrated that PCT was significantly correlated with the survival of the patients who had a positive blood culture. Figure 5 showed that patients with high PCT levels had a significantly low rate of survival as compared to those with a low PCT level. Bacteremia in PD patients: Role of PCT level.

According to previous studies, renal function appeared to influence the PCT levels (17). The cause of PCT elevation in patients with renal dysfunction could be its impaired renal or hepatic elimination or its increased production. Peripheral blood mononuclear cells release more PCT in patients with impaired renal function and those receiving renal replacement therapy. Thus, a higher cut off value for PCT was suggested for use in patients with impaired renal function (1, 18, 19). Similarly, in our study, the best cut off value of PCT for diagnosing bacterial infection was 1.3 ng/ml with 90.0% sensitivity, 70.3% specificity, 55.1% PPV and 94.5% NPV while for anaerobic bacteremia, the best cut off value was 1.29 ng/ml with 89.0% sensitivity, 67.1% specificity, 58.2% PPV, and 95.9% NPV for patients with PD.

Several studies have shown that a short TTP is associated with a significantly high mortality rate in patients with Staphylococcus aureus bloodstream infection (20, 21). In the present study, high PCT values are directly proportional to TTP. As the bacterial load increases, the severity of infection will be increased which in turn will raise the PCT levels resulting in short TTP, that is why PCT and TTP were significantly correlated which suggests that PCT can be a good prognostic marker for distinguishing bacteremia from non bacteremia. Some authors have provided convincing evidence that PCT is useful not only for detecting bacteremia but also for evaluating severity (predicting mortality) in patients with pneumonia in the ICU (22-24). Jensen et al (2006) found that a high maximum PCT level and the daily changes of PCT were the independent predictors of 90-day mortality in patients in the ICU. The CAPNETZ study reported a high prognostic value of PCT for predicting mortality in patients with CAP (22). In contrast, the GenIMS cohort study only found out the moderate additional value of PCT as compared with the pneumonia severity index and the CURB-65 score (24). To the best of our knowledge, however, no previous study from India has reported the PCT as the
prognostic marker for bacteremia in PD patients from a single institution.

Our results demonstrated that PCT was significantly correlated with the survival of patients who had positive blood cultures. Survival analysis showed that the patients with high PCT levels had a significantly lower rate of survival than those with a lower PCT levels. Since PCT secretions begin within four hours of stimulation and peak at 8 hours (7) and due to the assay time for PCT being only 20 minutes, the availability of its results becomes much earlier than the gold standard blood culture. The sensitive and the rapid aspects of serum PCT can be put to a better use by combining it with the gold standard blood culture test. The resulting effect of this combination embodies the attributes of both these tests and is instrumental in enabling a clinician in obtaining an early and a better diagnosis along with a subsequent decrease in the rates of both morbidity as well as mortality in Peritoneal dialysis patients. Thus the values of PCT can help nephrologists in identifying high-risk patients, which in turn could have a major impact on clinical practice. Its measurements may aid decision making, particularly in PD patients.

Conclusion

Therefore the study illustrates that the PCT is a very reliable biomarker that contributes to the early diagnosis of suspected blood stream aerobic and anaerobic infections and it is also useful in evaluating the severity and prognosis of blood stream infections, however, renal function should also be taken into account when using this biomarker.

References


