Procalcitonin as a Marker of Infection in Patients with Liver Cirrhosis Compared to C-Reactive Protein


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Abstract

Background: Bacterial infections are a major cause of morbidity and mortality among patients with liver cirrhosis. Procalcitonin (PCT) is a prohormone that has been used as a marker for the diagnosis of bacterial infections. It may have a role in infections related to liver cirrhosis. The present study aims to evaluate the role of Procalcitonin as a marker of infection in patients with liver cirrhosis.

Patients and Methods: Plasma level of Procalcitonin was measured in 60 age and sex matched patients with liver cirrhosis (40 with clinical signs of infections and 20 without clinical signs of infections), and 15 healthy control subjects.

Results: At cut off point of 0.6ng/ml, the sensitivity, specificity, positive predictive value (+PV) and negative predictive value (-PV) of procalcitonin were 87.50%, 83.33%, 85.7% and 85.4% respectively. Area under ROC Curve was 0.932. Area under ROC curve of procalcitonin was higher (0.932) than that of CRP (0.875). The sensitivity of procalcitonin was better than that of CRP with highly significant p-value <0.001.

Conclusions: Procalcitonin is a better useful marker in diagnosis of liver cirrhosis related infection rather than CRP.

Key Words: Cirrhosis – Infection – Procalcitonin.

Introduction

PROCALCITONIN (PCT) is a 116 amino acid protein, a calcitonin precursor, which is in healthy individuals produced by C type cells of thyroid gland [1].

The liver is a key source of PCT. However, production of PCT have been shown in a variety of organs, including liver, lung, kidney, adrenal tissue, monocytes, granulocytes, testis, prostate gland and small intestine [2,3,4]. Procalcitonin levels rise in bacterial, parasite and fungal infections [5]. Elevated procalcitonin levels appear only in inflammations of an infectious etiology with systemic signs. Therefore, procalcitonin determination is appropriate for the diagnosis of infections. Half-life of procalcitonin in serum is 20-24 hours, which makes it suitable for daily monitoring. Therefore, it is important in controlling the course of treatment. It can also distinguish bacterial infection from other types of inflammations [6].

The present study aims to evaluate the role of Procalcitonin as a marker of infection in patients with liver cirrhosis.

Patients and Methods

The study was conducted in Kasr Al-Ainy Hospital, Internal Medicine Department, Cairo University between February 2014 and May 2015. This case control study was conducted on 75 age and sex matched subjects divided into three groups:

- Group 1 (liver cirrhosis patients who are suffering from infection, 40 patients).
- Group 2 (liver cirrhosis patients without infection, 20 patients).
- Group 3 (control group, 15 patients).

Inclusion criteria:

- Infection should be assessed clinically and by presence of shift to the left in serum leukocytic differential count and the patient should have a positive bacterial culture.
- Non infection group should have no clinical signs of infection and show no shift to the left in serum leukocytic differential count.
- Control group should have no clinical signs of infection and otherwise healthy individuals.

Exclusion criteria:

- Age under 18 years.
- Patients without liver cirrhosis in group (1) and (2).
- Patients with other comorbid conditions.
- Patients with negative bacterial culture in group (1).

All candidates were presented to: Consent to participate in the study, full clinical history, physical examination, abdominal ultrasonography and laboratory assessment which included: Full blood count, bleeding profile, serum aspartate aminotransferase (AST) level, serum alanine aminotransferase (ALT) level, serum bilirubin, serum albumin, serum C-reactive protein, serum Procalcitonin, bacterial cultures according to the site of infection in group of infection. Assessment of severity of liver disease by Child [7] and MELD [8] scores. Signs of infections are according to definition of sepsis:

To diagnose sepsis the patient must exhibit at least two of the following [9]:
- Body temperature above (38.3°C) or below (36°C).
- Heart rate higher than 90 beats a minute.
- Respiratory rate higher than 20 breaths a minute.
- Probable or confirmed infection (total leucocytic count > 12,000 or <4000 or band > 10%).

Statistical analysis:

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12). Description of quantitative variables as mean, SD and range [10].

- Description of qualitative variables as number and percentage.
- Chi-square test was used to compare qualitative variables between groups.
- Unpaired t-test was used to compare quantitative variables, in parametric data (SD <50% mean).
- Mann Whitney test was used instead of t-test in non parametric data SD >50% mean.
- Spearman Correlation co-efficient test was used to rank variables versus each other positively or inversely p-value >0.05 insignificant p<0.05 significant and p<0.01 highly significant.

Results

The present study included 75 patients [40 liver cirrhosis patients with infections Group (1)], 20 liver cirrhosis patients without infections [Group (2)], who were diagnosed at Internal Medicine Department of Kasr Al-Ainy Hospital, Cairo University, compared to 15 healthy control subjects (Group 3). Procalcitonin and CRP were the two biomarkers compared here in our study among all groups.

- Mean of PCT was higher in liver cirrhosis patients with infection [Group (1)] (6.92±5.87) than in liver cirrhosis patients without infection [Group (2)] (0.63±1.13) with highly significant p-value. Also Mean of CRP was higher in liver cirrhosis patients with infection [Group (1)] (35.57±21.49) than in liver cirrhosis patients without infection group [Group (2)] (8.31±5.23) as shown in Table (1) and Fig. (4).

- Mean of CRP in liver cirrhosis patients with infection [Group (1)] (35.57±21.487) was higher than control group (Group 3) (8.202±7.851) with highly significant p-value <0.001.

- Mean of CRP in liver cirrhosis patients without infection [Group (2)] (8.3067±5.234) was slightly higher than control group [Group (3)] (8.202±7.851) with non-significant p-value >0.05, as shown in Table (2).

- Mean of PCT in liver cirrhosis patients with infection (Group 1) (6.918±5.86535) was higher than control group [Group (3)] (0.314±0.17377) but with highly significant p-value <0.001.

- Mean of PCT in liver cirrhosis patients without infection [Group (2)] (0.6335±1.12618) was higher than control group [Group (3)] (0.314±0.17377) but with non-significant p-value >0.05 as shown in Table (3).

- At cut off point of 0.6ng/ml, the sensitivity, specificity, positive predictive value (+PV) and negative predictive value (–PV) were 87.50%, 83.33%, 85.7% and 85.4% respectively with highly significant p-value <0.0001. Area under ROC Curve was 0.932 (Figs. 1,3).

- At cutoff point of 18mg/ml the sensitivity, specificity, positive predictive value (+PV) and negative predictive value (PV) for CRP were 75.00%, 88.10%, 87.8% and 75.7% respectively with highly significant p-value <0.0001 (Figs. 2,3). Area under ROC Curve was 0.875, so the PCT was superior to CRP in diagnosis of infection.

| Table (1): Significant difference between CRP and PCT in liver cirrhosis groups with infection [Group (1)] and without infection [Group (2)]. |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Group (1) | Group (2) | p value | Significance |
| no=40 | no=20 |
| Mean ± S.D | Mean ± S.D |
| CRP mg/L | 35.572±21.487 | 8.202±7.851 | <0.001 | H.S. |
| Procalcitonin ng/ml | 6.23±5.102 | 0.62±1.155 | <0.001 | H.S. |

H.S = Highly Significant.
Table (2): Significant difference of CRP in all groups in comparison with control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD of CRP</th>
<th>p Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis with infection</td>
<td>35.5725±21.487</td>
<td>&lt;0.001</td>
<td>H.S.</td>
</tr>
<tr>
<td>Liver cirrhosis without infection</td>
<td>8.3067±5.234</td>
<td>&gt;0.05</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control Group</td>
<td>8.202±7.8516</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H.S = Highly Significant. N.S = Non-Significant.

Table (3): Significant difference of PCT in all groups in comparison with control group.

<table>
<thead>
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<th>Parameters</th>
<th>Mean ± SD of PCT</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Liver cirrhosis with infection</td>
<td>6.9185±5.86535</td>
<td>&lt;0.001</td>
<td>H.S.</td>
</tr>
<tr>
<td>Liver cirrhosis without infection</td>
<td>0.6335±1.12618</td>
<td>&gt;0.05</td>
<td>N.S.</td>
</tr>
<tr>
<td>Control Group</td>
<td>0.3143±0.17377</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

H.S = Highly Significant. N.S = Non-Significant.

Discussion

Bacterial infections are a major cause of morbidity and mortality among patients with liver cirrhosis. Diagnosis of bacterial infections is sometimes challenging, because clinical manifestations of infections from different causative agents can be similar. For example, it may be difficult to differentiate viral from bacterial infections in different cases [11].

Incidence of bacterial infections in patients with liver disease is high. Due to a liver dysfunction, immune reactivity is significantly impaired. Therefore, bacterial infections causing sepsis, bacterial peritonitis, respiratory tract infections and urinary tract infections are more frequent [12].

Although the determination of procalcitonin appears to be one of the probable biomarkers in diagnosis of infection, the studies carried out make it difficult to establish conclusions on its real clinical usefulness. There is a debate about its use as a marker of infection in liver cirrhosis-related infection. Some authors found procalcitonin to be insignificant in diagnosis of infection in patients with liver cirrhosis [13] while others found it to be probably useful [14].

The present study aims to evaluate the role of Procalcitonin as a marker of infection in patients with liver cirrhosis.

Area under ROC curve of procalcitonin was higher (0.932) than that of CRP (0.875). The sensitivity of procalcitonin were better than that of CRP with highly significant p-value <0.001. This indicates the superiority of procalcitonin in diagnosis of infection rather than CRP.

Results of our study were in agreement with the study done by Chih-Huang et al. (2011). Ninety-eight patients were enrolled for analysis in Taiwan in 1 year to determine the diagnostic accuracy of procalcitonin measurement for bacterial infections in patients with liver cirrhosis. The cutoff that maximized Youden’s index was 0.49ng/mL for procalcitonin and 24.7mg/L for CRP. At these cutoffs, the sensitivity and specificity were 81.5, 87.3% for procalcitonin and 80.0, and 80.3% for CRP. As compared to the previous results, our study showed that procalcitonin has a better sensitivity (87.50%) and specificity (83.33%) and better area under ROC curve (0.932). For CRP, the sensitivity, specificity and area under ROC curve were (75.00%), (88.10%) and (0.857) respectively. Our results showed better diagnostic accuracy of procalcitonin over CRP measurement at near cutoff.
values and comparable number of patients to the previous study [15].

Results of the present study were also in agreement with the study done by Rahimkhani et al. (2013). Their aim was to survey PCT levels in patients with cirrhosis. Sixty-four patients with hepatic cirrhosis and 32 healthy blood donors were enrolled in their study. Serum procalcitonin levels were significantly higher in cirrhotic patients with bacterial infection (2.65±1.11 ng/ml) than those without infection (0.59±0.16 ng/ml, \( p=0.0001 \)). Their results were matched with the present study as it showed that mean of PCT was higher in liver cirrhosis with infection group (6.92±5.87) than in liver cirrhosis patients without infection group (0.63±1.13) but levels in the present study were higher, may be because the large number of infection group [12].

Results of our study were also in agreement with the study done by Le-Yong Yuan et al., who evaluated the diagnostic role of Procalcitonin (PCT), C-reactive protein (CRP), and white blood cells (WBCs) in diagnosis of spontaneous bacterial peritonitis (SBP) associated with chronic severe hepatitis B (CSHB). They measured PCT and CRP concentrations, WBC count, and other hematological parameters in 84 well-characterized patients with CSHB, of whom 42 had SBP. The optimal cutoff value for PCT was 0.48 ng/mL. Meanwhile, the sensitivity and specificity of PCT for CSHB patients with SBP were 95% and 79%, respectively, at the cutoff of 0.48 ng/mL. The optimal diagnostic cutoff value of CRP was 16.15 mg/L. The sensitivity and specificity of CRP in CSHB patients with SBP were 64% and 95%, respectively, at the cutoff of 16.15 mg/L. They also found better sensitivity of PCT over CRP but with better specificity of CRP over PCT at suggested cutoff values. When compared to our study, their results were near ours with very near cutoff values and number of sample but their study was only on spontaneous bacterial peritonitis patients [16].

Conclusion:
The results of the present study suggest that procalcitonin is able to diagnose bacterial infections in a satisfactory manner. It was found that the diagnostic accuracy of procalcitonin is more superior to that of C-reactive protein measurement in patients with liver cirrhosis. The suggested cutoff value of PCT is 0.6 ng/ml.

Recommendations:
Further study to determine if procalcitonin could be used safely as a guide for antibiotic treatment should be conducted in the future.

References
الملخص العربي

الالتهابات البكتيرية هي سبب رئيسي للمرض والوفيات بين المرضى الذين يعانون من تليف الكبد.

البروكالسيتونين هو طبقة الهورمون التي تم استخدامها كمعلم لتشخيص الالتهابات البكتيرية. وقد يكون له دور في الالتهابات المرتبطة بتليف الكبد. ولكن اختلاف الدراسات الطبية حول دوره في تشخيص العدوى في هؤلاء المرضى فإنه من ضروري إعادة تقييم هذا الدور.

وتهدف هذه الدراسة إلى تقسيم البروكالسيتونين كمعلم لإصابة بالعدوى في المرضى الذين يعانون من تليف الكبد.

وقد أجريت الدراسة لدينا طبقاً للمعايير التالية:

معايير التشخيص:

1. مجموعة (مرضي تليف الكبد الذين يعانون من العدوى، 40 مريضاً):
   - يجب أن يكون لديهم علامات سريرية للعدوى

2. المجموعة (مرضي تليف الكبد دون إصابة بالعدوى، 20 مريضاً):
   - يجب أن لا يكون لديهم علامات سريرية للعدوى

3. المجموعة (مجموعة المراقبة، 15 مشارك):
   - يجب أن لا يكون لديهم علامات سريرية للعدوى

4. على المستوى للمشاركة في الدراسة.

معايير الاستبعاد:

1. العمر أقل من 18 سنة.

2. المريض دون تليف الكبد في مجموعتين "1" و "2".

وفرض المشاركون إلى تأثير موضوع الفحص السريري الكاملاً، تحليل سيولة الدم، وظائف الكبد.

البروكالسيتونين في الدم، ملحوظات بكتيرية وفقاً لموقع الإصابة في مجموعات العدوى.

وقد تبين بعد التحليل الإحصائي:

أن معدل البروكالسيتونين كان أعلى في مجموعة تليف الكبد مع العدوى (6.97 ± 6.87) عن مرضى في مجموعة تليف الكبد دون العدوى (3.72 ± 3.72) مع وجود دالة إحصائية.

 عند معدل 0.62 نانومغريام/ مل (0.62 μg/mL) جمعية النسب العددية والمتوسطة والقيمة الإيجابية (PV) والقيمة التنبؤية السلبية (–PV) للبروكالسيتونين (0.85 ± 0.82) على التوالي.

كان أعلى في مجموعة تليف الكبد مع إصابة بالعدوى (4.75 ± 5.92) عن مرضى في مجموعة تليف الكبد دون العدوى (2.71 ± 2.71) مع وجود دالة إحصائية.

 عند معدل 18 غل/ مل (18 μg/mL) جمعية النسب العددية والمتوسطة والقيمة الإيجابية (PV) والقيمة التنبؤية السلبية (–PV) للبروكالسيتونين (0.85 ± 0.82) على التوالي.

وقد تكون المنطقة تحت المنحنى ROC (0.937 ± 0.085) من (0.85 إلى 0.92) مع وجود دالة إحصائية. وهذا يدل على فرق البروكالسيتونين في تشخيص العدوى مقارنة باختبار CRP.

ولذا أن البروكالسيتونين أدق وأفضل من CRP في تشخيص العدوى في مرضى تليف الكبد. وكان قيمة العدد المقترح للتشخيص هو 6.6 نانومغريام/ مل.