The Role of the Procalcitonin in Diagnosis of Neonatal Sepsis and Correlation Between Procalcitonin and C-Reactive Protein in these Patients

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Abstract: The goal of this study was to investigate the role of procalcitonin (PCT) in diagnosis of neonatal sepsis and its correlation with C-Reactive Protein (CRP). One hundred and seventeen neonates with the gestational age ≥ 35 weeks with clinically suspected diagnosis of neonatal sepsis were studied during one year from 2007 in Tabriz Children’s Hospital. Conventional sepsis workup was done in all cases and the diagnosis of neonatal sepsis was proved based on the results of blood culture. The serum procalcitonin was measured by quantitative Chemo-luminescence methods and the results were compared with CRP levels between the neonates with and without proven sepsis. The results showed among in 117 neonates with suspected sepsis 27 (23.1%) cases have positive blood culture (proven sepsis). The mean levels of PCT in neonates with and without proven sepsis was 4.42±6.66 vs. 2.06±4.03 ng mL⁻¹ and CRP 33.98±36.81 vs. 12.30±20.42 mg L⁻¹ were significantly higher in neonates with proven sepsis (p = 0.026 and p<0.001). The sensitivity, specificity, positive predictive value and negative predictive value of PCT (more than 2 ng mL⁻¹) were 66.7, 50, 28.6, 83.3 and CRP (more than 3.5 mg L⁻¹) were 70.4, 72.2, 43.2 and 89%, respectively, in diagnosis of neonatal sepsis. There was a meaningful correlation between the level of PCT and CRP in the sepsis group (r = 0.797, p<0.001). The results of the current study showed that more relying on the level of PCT and CRP for planning the management of neonates with suspected sepsis is not logical, but a negative result may be helpful in ruling it out.

Key words: Neonate, sepsis, procalcitonin, C-reactive protein

INTRODUCTION

Neonatal sepsis is invasive bacterial infection occurring during the first month of life. The incidence of culture-proven sepsis is approximately 2 per 1000 live birth and from the 7-13 % of neonates who are evaluated for neonatal sepsis, only 3-8% have culture-proven sepsis. The early signs of sepsis in the newborn are non-specific and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distension, seizure and jaundice. Therefore many newborns undergo diagnostic studies and the initiation of treatment before the presence of sepsis has been proven, because the mortality rate of untreated sepsis can be as high as 50% (Angus and Wax, 2001). Rapid diagnosis of neonatal sepsis is problematic because the first signs of this disease may be minimal and are similar to those of various non infectious processes, furthermore bacterial culture are time-consuming and other laboratory tests are either not available for routine use or lack sensitivity or specificity. In this situation neonates with risk factors for infection or clinical suspicion of infection are empirically treated with antibiotics. To avoid the unnecessary treatment of non infected patients an early sensitive and specific laboratory test would be helpful to guide clinicians in neonatal units in deciding whether or not to start administering antibiotics. Several leukocyte indices and acute phase protein levels have been evaluated for the diagnosis of sepsis and more recently measurement of multiple plasma cytokines (Hodge et al., 2004b) and leukocyte activation markers (Hodge et al., 2004a) have showed promising results. However to date no single laboratory test has provided rapid and reliable identification of infected neonates. This inability has led to a search for new diagnostic markers (Polin, 2003; Lopez Saster et al., 2007). Procalcitonin is the precursor protein of calcitonin and has no hormonal activity. It is a 116 amino-acid protein with a molecular mass of 14.5 kDa (Whicher et al., 2001). It was shown in healthy volunteers that PCT is detectable in the plasma two hours after the injection of a small amount of bacterial endotoxins, increasing rapidly in 6-8 h and reaching a plateau and then decreasing to normal levels after 24 h (Whicher et al., 2001; Dandona et al., 1994). PCT levels increase in sever sepsis.

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and its plasma concentration is related to the patients clinical condition and capacity of immune reaction. Serum PCT levels appeared to correlate with the severity of microbial invasions and decreased rapidly after appropriate antibiotic therapy. (Whitcher et al., 2001; Ghilani et al., 1989). It has been recently reported that PCT increases markedly in septic condition (Gendrel et al., 2000) and it appears to be a good predictor of infection severity (Muller et al., 2001). The results of recent studies suggest the usefulness of PCT for early diagnosis of neonatal sepsis (Blomemandahl et al., 2002; Franz et al., 1999), although other investigators have observed lack of accuracy for this marker (Koskenvuo et al., 2003; Lapillonne et al., 1998). CRP is one of the acute phase proteins, although it is a classical and sensitive marker of inflammation, it cannot be used to differentiate between bacterial and other infections (Jaye and Wistes, 1997). It is a disadvantage that CRP increases after PCT for the follow-up of the progression of the infection (Whitcher et al., 2001). Hatherill reported in critically ill children the admission procalcitonin is better diagnostic marker of infection than CRP or leukocyte count. A procalcitonin concentration of 2 ng mL\(^{-1}\) might be useful in differentiating severe bacterial disease in infant and children (Hatherill et al., 1999). Monneret study showed elevated PCT levels correlate with sepsis and that appropriate antibiotic therapy lowers it rapidly, they also found that CRP did not show a similar correlation (Monneret et al., 1997). The aim of our study was to determine the role of the procalcitonin in diagnosis of neonatal sepsis and correlation between procalcitonin and C-reactive protein in these patients.

**MATERIALS AND METHODS**

This is a retrospective cross-sectional study on 117 suspected sepsis neonates at the age of 0-28 days who were admitted in neonatal service of children hospital of Tabriz University Medical Sciences during April 2007 to April 2008. In this study we excluded all newborn with congenital anomaly, gestational age under 34 weeks, suspected haemorrhage and neonates delivered with asphyxia.

Before antibiotic therapy conventional sepsis workup was carried out in all cases including: CBC counts, ABG, Chest x-ray, Urine culture and analyzes, Lumbar puncture for CSF culture and biochemical analyzes and 0.5 mL blood sample with sterile method for blood culture. CRP was determined using an immunonephelometric methods (using BN II device, Germany).

Three milliliter blood sample was drawn from all neonates, and blood samples were centrifuged within 30 min of collection. Serum was stored at -20°C before analysis. PCT was measured by quantitative Chemo-Lumiance method (Diasorin, Germany). The neonates were divided in two groups regarding their laboratory results and general appearances, proven sepsis who had positive blood culture and suspected sepsis who had negative blood culture but had positive CRP and either neutropenia or thrombocytopenia and positive chest x-ray. The increase in PCT more than 2 ng mL\(^{-1}\) and CRP more than 3.5 mg L\(^{-1}\) were investigated in two groups and then correlation between serum PCT level and CRP was evaluated in these patients. Statistical analysis with the SPSS version 15 software, correlation between the variable and the statistical differences were analyzed using Pearsons, Chi-squared test, Mann-Whitney U test and Student t-test. The reliability of serum PCT and CRP concentration for the diagnosis of neonatal sepsis was calculated by Receiver Operating Characteristic (ROC) curves. Sensitivity, specificity and the likelihood ratio of a positive and negative result with the 95% Confidence Interval (CI) were calculated Statistical significant was set at (p<0.05).

The research review board and ethic committee of Tabriz University of Medical Sciences approved the study (Code No. 8528).

**RESULTS AND DISCUSSION**

From 117 term neonates 27 patients (group 1) had proven sepsis (blood culture positive) and 90 of them (group 2) had suspected sepsis (blood culture negative).

Mean variable comparison between two group is shown in Table 1.

As shown in Table 1, except PCT and CRP there are not statistically meaningful differences between two group. The mean level of PCT and CRP were significantly higher in neonates with proven sepsis as shown in Fig. 1 and 2.

Serum PCT level was higher in 18 cases of group 1 and 45 patients of group 2 (p = 0. 128), and also CRP level was higher in 19 cases of group I and 25 neonates of group 2 (p<0. 001).

Simultaneous increase in serum CRP and PCR was seen in 17 cases of group 1 and 19 patients of group 2 and this relationship was statistically meaningful in group 1 than other group (p<0. 001). The diagnostic value of PCT and CRP in neonatal sepsis is shown in Table 2.

ROC curves in PCT value for diagnosis of neonatal sepsis are depicted in Fig. 3. The area under the curve were 0.614 (95 CI, 47 to 75%). Cut off level with the optimum diagnostic efficiency derived from the ROC curve were 1. 36 ng mL\(^{-1}\) and the sensitivity and specificity of PCT in diagnosis of neonatal sepsis were
Table 1: Mean variable comparison between two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (No. 27)</th>
<th>Group 2 (No. 90)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.1±4.894</td>
<td>7.9±8.01</td>
<td>0.086</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>32</td>
<td>0.888</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>2715.9±412.31</td>
<td>2871.8±640.64</td>
<td>0.236</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>48.2±4.23</td>
<td>47.6±3.56</td>
<td>0.456</td>
</tr>
<tr>
<td>Head circumference</td>
<td>34.5±2.50</td>
<td>34.1±2.25</td>
<td>0.468</td>
</tr>
<tr>
<td>Positive CSF culture</td>
<td>2</td>
<td>0</td>
<td>0.999</td>
</tr>
<tr>
<td>Positive urine culture</td>
<td>1</td>
<td>2</td>
<td>0.548</td>
</tr>
<tr>
<td>WBC</td>
<td>10086.3±0.5384.27</td>
<td>11578.8±5874.44</td>
<td>0.244</td>
</tr>
<tr>
<td>Immature/Total</td>
<td>2.8±4.22</td>
<td>1.3±2.23</td>
<td>0.222</td>
</tr>
<tr>
<td>Platelet</td>
<td>181982.9±103213.18</td>
<td>222188.9±119856.55</td>
<td>0.118</td>
</tr>
<tr>
<td>Bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22.4±9.56</td>
<td>14.7±9.92</td>
<td>0.070</td>
</tr>
<tr>
<td>Direct</td>
<td>0.6±0.52</td>
<td>0.7±0.93</td>
<td>0.070</td>
</tr>
<tr>
<td>Positive CXR</td>
<td>10</td>
<td>33</td>
<td>0.972</td>
</tr>
<tr>
<td>Procalcitonin (ng mL⁻¹)</td>
<td>4.4±6.66</td>
<td>2.0±6.43</td>
<td>0.026</td>
</tr>
<tr>
<td>CRP (mg L⁻¹)</td>
<td>33.9±36.81</td>
<td>12.3±20.22</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2: The diagnostic value of PCT and CRP in neonatal sepsis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher PCT</td>
<td>66.7</td>
<td>50.0</td>
<td>28.6</td>
<td>83.3</td>
</tr>
<tr>
<td>Higher CRP</td>
<td>70.4</td>
<td>72.2</td>
<td>43.2</td>
<td>89.9</td>
</tr>
<tr>
<td>Higher PCT and CRP</td>
<td>63.0</td>
<td>78.9</td>
<td>47.2</td>
<td>87.7</td>
</tr>
<tr>
<td>Normal PCT and CRP</td>
<td>43.3</td>
<td>74.1</td>
<td>84.8</td>
<td>28.2</td>
</tr>
</tbody>
</table>

Fig. 1: Serum PCT level in neonates with and without proven sepsis

55/6, 63.3%, respectively. In Fig. 3 the CRP value for diagnosis of neonatal sepsis with regard to area under the ROC curve were 0.734 (95 CI, 62-85%). The cutoff level with the optimum diagnostic efficiency derived from the ROC curve for CRP were 4.86 mg L⁻¹ and the sensitivity and specificity of CRP in diagnosis of neonatal sepsis were 70.4 and 74.4%, respectively.

In this study there was meaningful correlation between the level of serum PCT and CRP in the sepsis group (r = 0.797, p<0.001) (Fig. 4).

Fig. 2: The level of serum CRP in neonates with and without proven sepsis

In the present study we investigated serum level of PCT and CRP in neonates with or without proven sepsis. The results of this study shows that mean level of these factors are higher in neonates with proven sepsis than those without sepsis, and these difference is statistically meaningful. Kocabas et al. (2007) study in 29 neonates with proven sepsis and 29 normal neonates showed that mean level of serum PCT and CRP is significantly higher in neonates with proven sepsis.
with confirmed sepsis based on positive blood culture results at a PCT cutoff level of greater than or equal to 2 ng mL⁻¹, the sensitivity and specificity, PPV and NPV were 88.9, 65.2, 40 and 95.7% and for CRP 55.6, 89.9, 58.8 and 88.6%, respectively. Ballot et al. (2004) studied 52 neonates with possible infection and only 13 neonates had definite infection, in these neonates sensitivity and negative predictive value of serum PCT was 89.5 and 95%, respectively, but they stated that although PCT was significantly related to the category of infection, it is not sufficiently reliable to be the sole marker of neonatal sepsis, PCT would be useful as part of full sepsis evaluation, but is relatively expensive. A negative PCT on presentation may rule out sepsis. Joram et al. (2006) investigated umbilical cord blood PCT and CRP concentration for early diagnosis of very early onset neonatal sepsis, they measured PCT and CRP concentration in umbilical cord blood of 197 neonates for evaluating their value as markers of infection. Sixteen of the neonates were infected, the sensitivity and specificity, PPV and NPV were respectively, 88.7, 98.7, 98.7 and 87.5 for PCT and 50, 94 and 67% for CRP. They believe that serum PCT in cord blood is useful as early marker of antenatal infection. Recently Vazquez et al. (2005) assessed PCT for the diagnosis of late-onset sepsis in 67 neonates. At a PCT cutoff value of 1.0 ng mL⁻¹ sensitivity was 97% and specificity 80% while with CRP sensitivity 72% and specificity 93%.

Turner et al. (2006) with using high cutoff levels for both PCT (2.3 ng mL⁻¹) and CRP (30 ng L⁻¹) in work up assess in 100 neonate with suspected sepsis. They found the specificity and positive predictive value for PCT and CRP was 97, 91 and 96, 87%, respectively, but had low sensitivity (48 and for CRP 41%) to detect neonatal sepsis, in this study area under the ROC curve was 0.74 and 0.73 for PCT and CRP, respectively. Chiesa et al. (1998) studied the reliability of PCT concentration in 28 infants who had severe early onset of neonatal sepsis. They found sensitivity, specificity, PPV and NPV were 92.6, 97.5, 94.3 and 96.8%, respectively, they also found that 24 infants had PCT levels higher than normal at the time of diagnosis. However at that time only 13 of them had high CRP levels. Hatherill et al. (1999) study showed the sensitivity and specificity of serum PCT level were 92.6 and 97.5%, respectively, in diagnosis of early onset neonatal sepsis and 100% in neonates with late onset sepsis. We did not consider the type of neonatal sepsis in present study. In this study the sensitivity and specificity of CRP was more than PCT, this was due to delayed increase in CRP level in comparison to PCT, in other words, in early onset neonatal sepsis PCT releases earlier than CRP.
The results of the reports are various, the causes of these differences are age of newborns, methods of PCT and CRP measurement and determination of cutoff levels of them, sepsis workup technic, amount of blood sample taken for blood culture, previous use of antibiotic and organism involved in sepsis that all may interfere in results.

CONCLUSION

The results of the current study showed more relying on the level of PCT and CRP for planning the management of neonates with suspected sepsis is not logical, but a negative results may be helpful in ruling it out.

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REFERENCES


