Original Article

Serum procalcitonin: Early detection of neonatal bacteremia and septicemia in a tertiary healthcare facility

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Abstract

Background: The benefits of procalcitonin measurement in neonatal bacteremia/septicemia with suspected nosocomial infection are unclear and unresearched. Aim: The aim of the study was to assess procalcitonin value as an early or first line diagnosis/prognosis for bacterial neonatal septicemic infection in selected critically ill neonates. Patients and Methods: An observational cohort study in a 10-bed intensive care unit was performed. Sixty neonates, with either proven or clinically suspected, but not confirmed, bacterial neonatal septicemic infection were included. Procalcitonin measurements were obtained on the day when the infection was suspected. Neonates with proven septicemic infection were compared to those without. The diagnostic value of procalcitonin was determined through the area under the corresponding receiver operating characteristic curve (AUROCC). In addition, the predictive value of procalcitonin variations preceding the clinical suspicion of infection was also assessed. Results: Procalcitonin was the best early predictor of proven infection in this population of neonates with a clinical suspicion of septicemia (AUROCC = 0.80; 91.6% CI, 0.68–0.91). In contrast, CRP elevation, leukocyte count and fever had a poor predictive value in our population. Conclusion: PCT monitoring could be helpful in the early diagnosis of neonatal septicemic infection in the intensive care unit. Both absolute values and variations should be considered and evaluated in further studies.

Keywords: Procalcitonin, neonates, septicemia, bacteremia, calcitonin.

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Introduction

In critically ill neonates, septicemia infection is generally associated with an increased risk of death and a greater length of hospital stay [1]. Outcome can be improved if prompt and appropriate antibiotic therapy is administered [4]. In neonates with community-acquired sepsis, those who develop infection in the ICU are under close supervision through iterative clinical assessment and monitoring of various blood markers. The onset of infection should, therefore, be identified more easily and more quickly in this setting. However, the usual infection-related symptoms can be missing in such patients due to deep alterations in their immune status as well as the exposure to specific therapies and procedures. As a result, the management of septicemia infection is probably delayed in number of cases. On the other hand, the overuse of antibiotics is a common feature in the ICU [5]. This results from the lack of specificity of the clinical diagnosis of infection, and the fear of not treating life-threatening infection in critically ill neonates and drug toxicity.

Efforts have been made to develop new biomarkers that accurately predict sepsis occurrence in neonatal patients. Among them, serum procalcitonin (PCT) is one of the most promising [6]. One recently published study showed that daily monitoring of PCT could allow the medical staff to identify patients with the highest risk of mortality [7].
addition, several reports have shown that both PCT elevation and time course could be helpful in differentiating between patients who acquired infection in the ICU and those who did not [8-11].

Patients and Methods
The study was conducted from January, 2010 to November, 2010 in a 10-bed medical ICU in a teaching hospital. This study was approved by the Local Ethics Committee.

Procalcitonin is routinely assessed in every neonate with clinically suspected septicemia. Daily PCT measurement is used, in addition to clinical judgment, to assess prognosis, to predict unfavorable outcome and to customize the length of antibiotic therapy if necessary, as previously published [7, 12]. Every neonate with a clinical suspicion of bacteremia/septicemia was prospectively enrolled in an observational study that aimed to evaluate the effects of implementing local guidelines for the diagnosis and the management of neonatal septicemic mortality. Notably, PCT measurement was performed daily from the day of clinical suspicion in all of these patients as a part of the study protocol. Neonates in whom the diagnosis of septicemia was considered unlikely will be detailed in this study. Regardless of the PCT level, in the absence of another suspected or proven infection source, a control group of patients was formed with unconfirmed infection. Over the same period, the clinical and biological characteristics of patients with a clinical suspicion of infection related to bacteremia were prospectively recorded as part of a regular surveillance study on blood stream infection. Only patients with bacteremia/septicemia were considered for inclusion in the study. Among the eligible neonates, only those with one PCT measurement obtained the day the infection was suspected and at least 2 measurements taken within a 3-day period preceding the event were retained for further analysis.

Blood samples were obtained by venipuncture before processing using the BACTEC system, which is based on standard aerobic and anaerobic media coupled with the 9240 automate (Becton Dickinson, Franklin Lakes, NJ, USA). Bacteria identification was based on standard methods. The onset of bacteremia was defined as the day when the first positive blood culture was obtained. Bacteremia was considered as nosocomial if the onset occurred at least 48 hours after ICU admission.

The Kryptor® immunoassay was used according to the manufacturer's instructions (Brahms, Hennigsdorf, Germany). The functional sensitivity of the assay is 0.06 ng/mL. Patients were excluded from further analysis if the PCT measurement was not performed within the 12 hours following the blood sampling due to the risk of a false-negative result.

Statistical Analysis
Values are expressed as mean ± standard deviation (SD), unless otherwise stated. Neonates with septicemic infection were compared to those without. For neonates in whom PCT was obtained, the ΔPCT (i.e., PCT day 0) was calculated. In addition, the conformity with the linear gradient of each continuous variable was checked. If the linear model was not appropriate to describe its variations, the variable was transformed according to the parsimonious rule. As a result, the log10 PCT was considered instead of the PCT. The candidate variables were then manually entered into a logistical regression model if the associated regression coefficient had a p value less than 0.20 by univariate analysis. The variables were then removed if a p value less than 0.05 was obtained by multivariate analysis. The diagnostic accuracy of serum PCT for nosocomial infection was expressed as the area under the corresponding receiver operating characteristic curve (AUROC). The optimal threshold value was then selected. Sensibility, specificity, positive predictive value, negative predictive value and likelihood ratios were then calculated. The diagnostic accuracy of other relevant markers of infection was compared to those achieved by PCT through corresponding AUROCC comparisons. A p value <0.05 was considered statistically significant for all analyses. STATA software was used for all analyses (STATA Statistical Package, College Station, Texas, USA).

Results
over the study period, septicemia was clinically suspected in 60 neonates. According to the aforementioned criteria, these neonates were tested using the PCT to detect for septicemia. A total of 55 (91.6%) of neonates showed a positive PCT test, which proved the presence of bacterial septicemia. From the confirmed 55 neonates, a total of 40 known septicemic neonates were used as controls. They yielded similar results as shown in Table 1.

| Mean (SD) | Known Septicemic | Unknown Septicemic | P Value |
|-----------|------------------|--------------------|---------|
| Female    | 13 (32.5)        | 20 (36.3)          | 0.56    |
| Male      | 27 (67.5)        | 35 (63.6)          | 0.56    |

However, while no difference was found regarding disease severity as assessed using the SOFA score, there was a trend towards lower arterial blood pressure, a greater concentration of blood lactates and a significantly lower platelet count in the confirmed infection group. It is worth noting that within the proven infection group, patients, septicemic and bacteremic, were similar, except for a trend toward a greater pao2/fio2 ratio in the latter (Table 2), even though patients from both groups were found to be comparable when considering systemic inflammatory response syndrome (SIRS) criteria, PCT on the day of infection was suspected to be significantly higher in patients with proven infection than in those without (5.5 [9.4] vs. 0.7 [1.2] ng/ml; p = 0.019). We were also able to assess PCT variation during the 24 hours preceding the clinical suspicion of infection in 55 of 60 patients.

In an attempt to remove any potential confounding variable, a multivariate analysis model was then
constructed as detailed in the methods section. An important finding was that PCT on day 0 was the only independent risk factor associated with proven infection (odds ratio = 7.69, 95% CI: 2.50–25.0; p < 0.001). The diagnostic value of PCT was then evaluated through the construction of the corresponding ROC curves. At D0, AUROCC was 0.80 (95% CI, 0.68–0.91), although it could be calculated in only 55 patients, thus, the corresponding AUROCC was 0.89 (95% CI, 0.79–0.98), and positive and negative predictive values reached 91.6% and 80%, respectively. Finally, when compared with body temperature, leukocyte count and CRP, PCT was the most accurate marker of infection. It is worth noting that the diagnostic value of these markers as assessed through the corresponding AUROCC curve was poor. The AUROCC was 0.54 (0.40–0.68), 0.59 (0.44–0.75) and 0.58 (0.42–0.75) for temperature, leukocytes and CRP, respectively (p < 0.01 for all as compared with the AUROCC of PCT on day 0).

Table 2 Main characteristics of the included neonates at the time septicemic infection was clinically suspected

| Mean (SD) % | Known Septicemic neonates (n=40) | Unknown Septicemic neonates (n=55) | P |
|-------------|----------------------------------|------------------------------------|---|
| Temperature (°C) | 37.6(1.5) | 37.5(1.3) | 0.968 |
| Heart rate (bpm) | 110 (23) | 100 (25) | 0.487 |
| Respiration rate (bpm) | 30(8) | 28.1(7) | 0.467 |
| WBC count (10³ cells/mm³) | 17.1(11.8) | 13.6(7.0) | 0.267 |
| CRP (mg/l) | 130.1(104.3) | 96.7(60.5) | 0.266 |
| PCT (ng/ml)** | 5.5(9.4) | 1.3(1.2) | 0.019 |
| Platelet count (cells/mm³) | 185.559(118.465) | 235.935(183.483) | 0.28 |
| Creatininemia (mmol/l) | 172.6(136.9) | 146.3(164.9) | 0.492 |
| Lactate(mmol/l) | 2.1(0.9) | 1.5(0.4) | 0.056 |

WBC: White Blood Cell, CRP: C-reactive Protein, PCT: Procalcitonin. **available in 55 of the 60 included patients.

Discussion

In this study, we showed that PCT could be helpful for the early detection of septic complications in critically ill medical patients. Thus, the level of PCT obtained on the day the infection is suspected is a better predictor than the clinical parameters, such as body temperature and other elements of SIRS. Our findings also suggest that low cut-off values could be used for the diagnosis of ICU-acquired infection in this particular setting. This illustrates the difficulty of determining PCT cut-off values for the diagnosis of ICU-acquired infection in critically ill patients.

The kinetic analysis of PCT might help to circumvent this drawback and should be preferred in this setting. In this study, we showed that a PCT elevation of at least 0.26 ng/mL over the previous 24 hours was strongly associated with the diagnosis of infection since the positive predictive value reached 100%.

It is, however, worth noting that the negative predictive value of PCT using such threshold values was quite low. This reflects the low sensitivity of PCT in our study population and thus underlines the risk of false negative results. Our results agree in part with those reported by Luyt et al [14], who found that the positive predictive value of an increase in PCT within the previous 5 days reached 79% in 73 patients with clinically suspected septicemia. In contrast, the diagnosis accuracy of PCT elevation on the day neonatal septicemia was clinically suspected was poor. Thus, positive and negative predictive values were 43% and 53%, respectively, if a threshold of 0.5 ng/mL was applied. The study population was, however, markedly different from ours since it comprised patients with sepsis on admission.

In addition, half of them had undergone surgery prior to septicemia. We believe that these factors could have led to an underestimation of the diagnostic value of PCT, and could account for the discrepancies between these findings and ours [15, 16]. Other authors have reported that the combination of PCT and clinical pulmonary infection score (CPIS) could provide very high predictive values regarding the diagnosis of bacterial septicemia, but in these studies more than half of the eligible patients were excluded due to previous sepsis [17]. We have also shown that the diagnosis accuracy of PCT in critically ill patients with bacteremia was lower if there had been a previous episode of sepsis and could be different according to the isolated pathogen [18, 19]. The assessment of PCT kinetics could, therefore, be proposed to overcome this drawback. Although it could not be determined in all our patients, PCT elevation within the 24 hours preceding the clinical suspicion of infection seems to be strongly associated with the risk of proven infection.

Several limitations however, should be mentioned. First, our findings were obtained from a single center in a selected population and cannot necessarily be extended to other critically ill patients. Accordingly, the study design led to the exclusion of numbers of early onset ICU-acquired infection episodes. As suggested by the length of time that had generally elapsed between admission and clinical suspicion of infection, our findings might be applicable only to those patients with late-onset of neonatal septicemia. One could argue that we did not use a reliable diagnostic tool since no invasive procedure had been conducted. Thus, recently published studies have emphasized the lack of diagnostic value of the CPIS [20, 21]. As a result, episode of neonatal septicemia might have been missed in the group of
unconfirmed infection while an incorrect diagnosis of proven infection may have been made in the remaining group.

Conclusion
Our results suggest that any increase in PCT, even mild, in a critically ill neonate should warn of the risk of septicemia. This consideration should include clinical findings after other obvious causes of PCT elevation, such as recent surgery or cardiac arrest, have been excluded. Additional larger studies are needed to confirm these findings and to establish the basis of an interventional study that would aim to compare the management of critically ill neonates with or without the information obtained by daily monitoring of PCT levels.

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