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Research

Diagnostic utility of procalcitonin versus C-reactive protein as markers for early-onset neonatal sepsis at Korle-Bu Teaching Hospital

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Abstract

Introduction: Symptoms of sepsis are non-specific among neonates and diagnosis requires a high index of suspicion. The study sought to evaluate the utility of procalcitonin (PCT) versus C-reactive protein (CRP) in diagnosing early-onset neonatal sepsis. **Methods:** This was a cross-sectional study in which neonates admitted to the neonatal intensive care unit, with signs suggesting sepsis were categorized according to an adapted criteria from Tollner's sepsis score and case definition of bloodstream infection as: "highly probable", "probable" and "less probable". Laboratory investigations including blood culture, complete blood count, PCT and CRP levels were done before first antimicrobial drug administration. **Results:** A total of 62 neonates less than 12 hours postnatal age (0.16-9.82 hours) were recruited. Proportion of neonates with PCT>2 ng/mL was 91% (20/22) in the "highly probable" group compared to 31.6% (6/19) in the "probable group" ($p<0.001$). Neonates with CRP>5 mg/L was 54.4% (12/22) in the "highly probable" group compared to 26.3% (5/19) in the "probable group" ($p = 0.07$). The receiver operator characteristics for PCT and CRP were; sensitivity (87.5% vrs 50%), specificity (63.0% vrs 72.2%), positive predictive value (44.1% vrs 37.5%) and negative predictive value (93.8% vrs 81.3%), respectively. **Conclusion:** PCT was a better predictive marker for neonatal sepsis within the first 12 hours of life than CRP in this setting, however, its low specificity relative to CRP suggests that neonates without patent infection are more likely to be incorrectly diagnosed with sepsis using this test.

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Introduction

Neonatal sepsis represents an important cause of morbidity and mortality especially in low-resource settings. Early diagnosis and prompt treatment of neonatal sepsis improves outcome [1]. However, the diagnosis of neonatal sepsis is complicated by many factors, including the non-specific clinical symptomatology and absence of specific biomarkers for diagnosis. Although blood culture remains the gold standard for diagnosis, the high false negative rate [2] and delay in obtaining results, places limitations on its clinical utility, thus the need for additional methods and continuous validation for existing markers in neonatal populations. C-reactive protein (CRP), an acute-phase reactant of hepatic origin that increases following secretion of interlukin-6 from macrophages and T-cells [3, 4], is elevated in acute inflammatory conditions, including infection. CRP is a valuable screening marker for the diagnosis of neonatal sepsis [5, 6], however, the time needed for its release, the non-specific response to inflammation, as well as variations in levels depending on physiological state (e.g birth weight or gestational age) [7-10], exerts a limitation on the use of CRP as a marker for neonatal sepsis diagnosis. Furthermore, CRP level has been shown to be low or normal in infants infected with coagulase-negative staphylococcus [11] and the magnitude of the CRP response is known overall to be higher in Gram-negative compared to Gram-positive infections [7].

Procalcitonin (PCT), a pro-hormone of calcitonin, synthesized by thyroid C cells [12] and which level increases markedly in septic conditions [13], is considered by some as a more sensitive marker than CRP in the early identification of bacterial infection in neonates [14, 15]. After exposure to bacterial agents, PCT levels increase within 3-4 hours, while CRP levels increase 12-18 hours later [16]. However, the role of these two markers in diagnosis of neonatal sepsis remain contentious [17, 18]: procalcitonin levels have been shown to vary between preterm and late-preterm neonates [19-21]. In term neonates, PCT demonstrates age-specific variation between the time of birth up to 48 hours [22], suggesting that cut-off levels of this acute-phase reactant should be age-dependent. Nonetheless, the features of physiological changes and reference in various infant populations have not been extensively studied. The incidence of early-onset neonatal sepsis vary between countries and study centers [23]. Also, depending on etiological agents, Gram-positive or Gram-negative bacteria, inflammatory response to infection could vary [24]. The heterogeneity of responses as well as difficulties in adopting a uniform definition for neonatal sepsis underlines the need to generate data from different settings in determining cut-off values of acute-phase reactants in the diagnosis of neonatal sepsis. Early-onset neonatal sepsis is commonly associated with co-morbid conditions but studies conducted to evaluate diagnostic utility of CRP and/or PCT rarely exclude confounders like perinatal asphyxia or meconium aspiration, which could affect predictive accuracy [25-27]. This study investigated the utility of CRP and PCT in neonates with suspected sepsis, excluding possible confounders and compared levels of these acute-phase reactants with clinical data and blood culture results.

Methods

Study design and site: This was a cross-sectional study, a sub-component of a larger study that evaluated the disposition of amikacin in neonates with suspected sepsis at the Neonatal Intensive Care Unit (NICU), Korle-Bu Teaching Hospital, Accra, Ghana, from November 2013 to June 2014. The full details of the larger study has been reported elsewhere [**28**]. The NICU is a 55-bed tertiary unit that admits annually an average of 2000 sick and preterm neonates mainly from southern Ghana. The NICU restricts admission to neonates with postnatal age less than 48 hours, unless in exceptional situations.

Criteria for inclusion and exclusion: Admitted neonates that fulfilled criteria (described below) were purposely selected. Eligible neonates were categorized as; "highly probable", "probable" and "less probable" neonatal sepsis, based on an adapted criteria from Tollner's sepsis score [29] and case definition of bloodstream infection by Vergnano et al [30] (Table 1).

Inclusion: neonates with maternal risk factors (prolonged rupture of amniotic membrane >18 hrs, chorioamnionitis), neonatal risk factors (low birth weight and premature birth) and clinical symptoms (feeding intolerance, lethargy, temperature instability, tachypnea, bradycardia, tachycardia, abdominal distension or vomiting) and deemed by the admitting physician to have a presumptive diagnosis of sepsis, were enrolled.

Exclusion: neonates presenting with meconium aspiration, perinatal asphyxia or neonates who required resuscitation for any reason, were excluded.

Blood sampling and laboratory analysis: After initial examination by study pediatrician and before first antimicrobial drug dose, blood samples were taken from recruited neonates, for the following investigations: blood culture (1-2 mL), full blood count (0.5 mL), CRP and PCT (0.5 mL). The sample for culture was collected into pediatric culture vials (BACTEC Peds plus/F, Becton-Dickinson, Gauteng, South Africa) and those for full blood count, CRP and PCT analysis into EDTA and gel microtainer tubes, respectively. The samples for measurement of CRP and PCT levels were immediately centrifuged to obtain serum. Blood culture was done using a fully automated BACTEC 9240 blood culture system (Becton Dickinson Diagnostic Instrument Systems, Sparks, Maryland). Isolates from positive bottles were sub-cultivated and identified using biochemical methods. Briefly, Gram-positive bacteria were identified by catalase, slide and tube coagulase test and Gram-negative by API 20E and 20NE (BioMerieux, France). Antibiotic susceptibility tests were done using the disc diffusion method on Mueller-Hinton agar (Oxoid, UK), in accordance with Clinical Laboratory Standards Institute (CLSI) criteria. Complete blood count was done by means of a Sysmex Autoanalyzer (Sysmex KX-21N, Sysmex Corporation, Kobe, Japan). CRP assay was performed with a BNII automated system (Dade-Behring Inc, Newark, Delaware), according to manufacturer's instructions. The assay uses particle-enhanced immunonephelometry to quantify CRP in serum samples [31]. Limit of detection of assay was 0.17 mg/L. Electrochemiluminescence immunoassay, which is based on a sandwich principle [32], was used to analyze PCT in serum of neonates. An automated Elecsys (Roche Diagnostics, Rotkreuz, Switzerland) was used for this purpose according to manufacturer's instructions. Limit of detection of assay was 0.1 ng/mL.

Ethical issues: Approval of this research was from the Ethical and Protocol Review Committee of the School of Medicine and Dentistry, University of Ghana (Protocol ID: MS-Et/M.8-P.5.3/2011-2012). Written informed consent was obtained from parents of all recruited neonates.

Statistical analysis: One-way ANOVA was used to compare the means of selected clinical and laboratory parameters (PCT and CRP levels) between the "highly probable", "probable" and "less

probable'' neonatal sepsis groups. Chi-square was used to compare proportions of neonates with elevated PCT and CRP among the groups. Blood culture was used as the gold standard for receiver operator characteristics (ROC) of PCT and CRP. Area under the ROC curve (AUC) for PCT and CRP were compared using Chi-square. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics and outcome: A total of 62 neonates fulfilled criteria for inclusion and were categorized as: highly probable (22 neonates), probable (19 neonates) and less probable (21 neonates) sepsis. All neonates were recruited within 12 hours after birth (0.16-9.82 hours) and prior to first antimicrobial drug dose. Selected baseline demographic and clinical parameters are shown in Table 2. The overall mortality was 9.7% (n=6) and case fatality per group was 13.6% (n=3), 10.5% (n=2) and 4.8% (n=1) in the highly probable, probable and less probable groups, respectively. All neonates who died were less than 34 weeks gestational age and weighed less than 1500 grams.

PCT and CRP levels between groups: Mean PCT levels were significantly different between the three groups. The PCT levels followed the order: ''highly probable'' > ''probable'' > ''less probable'' groups (Table 2). Mean CRP levels showed a similar trend, however, this difference did not attain statistical significance (p = 0.08). The PCT levels were elevated (>2 ng/mL) in 91% (20/22) of neonates in the highly probable group compared to 31.6% (6/19) in the probable group (p<0.001). The proportion of neonates with elevated (>5 mg/L) CRP levels was higher in the highly probable group (54.5%; 12/22) compared to probable (26.3%; 5/19), but the difference (p=0.07) showed only a trend towards but did not attain statistical significance.

Positive blood culture and sepsis risk score: In all, 36.4% (8/22) of neonates in the ''highly probable'' group had positive blood cultures. Among the ''highly probable'' neonatal sepsis risk group, there was no statistically significant difference in mean (SD) PCT (4.3 (2.4) ng/mL versus 4.1 (0.6) ng/mL; p = 0.9) and CRP (11.3 (21.7) mg/L versus 5.2 (1.2) mg/L; p = 0.3) between those with positive blood cultures and those with negative blood cultures respectively. Overall, CRP levels were more reflective of blood culture positivity even though the difference was not statistically significant. Clinical characteristics, PCT and CRP levels of neonates with positive blood culture are shown in Table 3.

Diagnostic accuracy of PCT and CRP: The receiver operator characteristic curves (ROCs) of PCT and CRP are shown in Figure 1. The area under the receiver operating characteristic curve (AUC) for PCT was 0.646 compared to that of 0.569 for CRP (p = 0.09) and these were at optimal thresholds of 2 ng/mL and 5 mg/L for PCT and CRP, respectively. Using the above thresholds, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of PCT and CRP were: 87.5% versus 50.0%, 63.0% versus 72.2%, 44.1% versus 37.5% and 93.8% versus 81.3%, respectively.

Discussion

Diagnosis of neonatal sepsis remains a difficult task due to the non-specific nature of clinical signs and symptoms in this age group. As sepsis remains a major cause of neonatal deaths, the standard of care includes the use of empiric antibiotic treatment on wide indications. As a result, the fear of missing a case of neonatal infection invariably leads to an overuse of antibiotics at NICUs. To ensure antimicrobial accountability while reducing neonatal deaths, there is the need for newer, faster and reliable markers of infection, and continuous validation of existing ones. In the current study, the proportion of neonates with elevated PCT in the highly probable sepsis group was significantly different compared with the probable sepsis group. Generally, serum PCT levels begin to rise 4 hours after exposure to bacterial endotoxin, peaks at 6-8 hours, and remain raised for at least 24 hours [33]. On the other hand, CRP levels start to increase 4 to 6 hours later than PCT and reaches peak 36 hours later [34]. Thus, the high proportion of neonates in the highly probable sepsis group with elevated PCT, relative to CRP, is consistent with the kinetics of these biomarkers after exposure to bacterial agents [33, 34]. PCT levels greater than 10 ng/mL have been associated with high mortality [35], however, the PCT levels of all neonates who died in this study were less than 10 ng/mL. A possible reason for this observation could be the fact that all neonates who died were delivered preterm [36].

The higher AUC of the ROC curve for PCT compared to that of CRP is consistent with studies [37, 38], on early-onset neonatal sepsis. In contrast Park et al [39], studied newborns with postnatal age ranging between 4 and 30 days and reported a lower AUC (0.803) of PCT compared to CRP (0.951). These dissimilarities could be due to differences in postnatal age and the kinetics of these biomarkers. PCT showed higher sensitivity, PPV and NPV compared to CRP in this study. These results, together with others [37, 38, 40], suggest that PCT is a more sensitive marker for sepsis diagnosis within the first 24 hours of life. The utility of the high NPV of PCT in this study may be its potential in excluding neonates without sepsis. This may be helpful in decision-making about early discontinuation of antibiotics in neonates without strong clinical indicators of sepsis. PCT is a relatively more reliable diagnostic marker for diagnosis of early-onset neonatal sepsis, the cost of the test precludes its routine use in clinical management of sepsis [41]. Therefore, a cost benefit analysis is recommended if PCT is to be used as diagnostic marker, alone or in combination with others, for sepsis at NICUs, especially in low-resource settings. A limitation of this study is the weakness inherent in the adapted criteria used for sepsis classification. One example is the criteria based on tachypnea (rate >60 cpm), as most neonates born preterm (especially <34 weeks gestation) have some degree of respiratory distress syndrome, which can manifest with tachypnea in the absence of sepsis. The use of blood culture in the sepsis definition in this age group is another limitation because of its low sensitivity given the limited volume of blood used for the test.

Conclusion

In summary, this study has shown that within the first 12 hours of life, PCT is a more reliable acute phase reactant in diagnosing neonates with sepsis than CRP. The use of PCT during the first 12 hours of life may limit number of neonates started on antibiotics due to suspected risk of sepsis when there are no strong clinical indicators of illness. Limiting unnecessary use of antibiotics in NICUs in low-resource settings will improve efficiency in clinical care and decrease the rising trend of antimicrobial resistance.

What is known about this topic

The role of PCT and CRP, in the diagnosis of neonatal sepsis remain controversial;
CRP is a valuable screening marker for the diagnosis of neonatal sepsis, however, there are variations in levels depending on physiological state of neonate (e.g birth weight or gestational age).

What this study adds

Within the first 12 hours of life, PCT is a more reliable acute phase reactant in diagnosing neonates with sepsis than CRP in this cohort of neonates;
Although PCT has low specificity (relative to CRP), it may improve antimicrobial use accountability in low-income countries as clinicians would treat fewer newborns without sepsis than current practice where most newborns in NICUs are given antibiotics.

Competing interests

The authors' declare no conflicts of interest.

Authors' contributions

Design of study was by Seth Kwabena Amponsah, George Obeng Adjei, Christabel Enweronu-Laryea, and Jorgen Anders Lindholm Kurtzhals. Clinical work of study was coordinated by Seth Kwabena Amponsah and Joan Woode, under the supervision of Christabel Enweronu-Laryea and George Obeng Adjei. The laboratory work was coordinated by Seth Kwabena Amponsah and Abdul Malik Sulley, under the supervision of George Obeng Adjei and Jorgen Anders Lindholm Kurtzhals. All authors contributed to the writing of manuscript and approved final version.

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Table 1: Criteria for classification based on Tollner's sepsis score and case definition of bloodstream infection	
I	Positive blood culture (pathogenic microorganism)
II	Negative blood culture
III	Maternal risk (prolonged premature rapture of membranes > 18 hours)
IV	Tachycardia (Heart rate > 160 bpm) or Bradycardia (Heart rate < 100 bpm)
V	Tachypnea (Rate > 60 cpm)
VI	Leukopenia (WBC < 5 x 10^9/L) or Leukocytosis (WBC > 25 x 10^9/L)
VII	Thrombocytopenia (platelet < 150 x 10^9/L)
Highly probable (Group 1): I or II, plus > 3 of remaining criteria **Probable (Group 2)**: II, plus 2 or 3 of remaining criteria (I excluded) **Less probable (Group 3)**: II, plus < 2 of remaining criteria (I excluded)	

Table 2: Characteristics [mean (SD)] of recruited neonates with clinical suspicion of sepsis				
Characteristic	**Highly probable (n = 22)**	**Probable (n = 19)**	**Less probable (n = 21)**	***p-value***
Gestational age (wks)	33.2 (4.3)	32.5 (4.2)	34.8 (4.3)	0.2
Birth weight (kg)	2.1 (0.9)	1.7 (0.7)	2.4 (1.1)	0.08
Sampling time postnatal hours	5.5 (3.3)	4.1 (2.8)	6. (2.2)	0.1
PCT (ng/mL)	4.2 (2.2)	1.5 (1.2)	0.8 (0.6)	<0.001
CRP (mg/L)	7.4 (13.4)	2.9 (3.9)	1.9 (1.8)	0.08

Table 3: Selected characteristics of neonates with positive blood culture in the highly probable sepsis group						
N	Isolate	GA (weeks)	BW (kg)	PNA (hours)	CRP (mg/L)	PCT (ng/mL)
1	*Burkholderia cepacia*	26	1.1	1.3	0.6	2.3
2	*Klebsiella pneumonia 2*	26	0.9	1	2.5	3.1
3	*Streptococcus viridians*	30	1.7	0.9	1.6	8.1
4	*Escherichia coli*	31	1.5	3.2	0.4	1.9
5	*Streptococcus agalactiae 2*	33	1.9	0.4	64.5	2.5
6	*Klebsiella pneumonia 1*	33	1.6	0.9	5.2	7.5
7	*Acinetobacter baumannii*	38	3.2	3.3	7.1	3.7
8	*Streptococcus agalactiae 1*	38	3.2	2.3	8.1	4.9
GA = Gestational age, BW = Birth weight, PNA = Postnatal age						

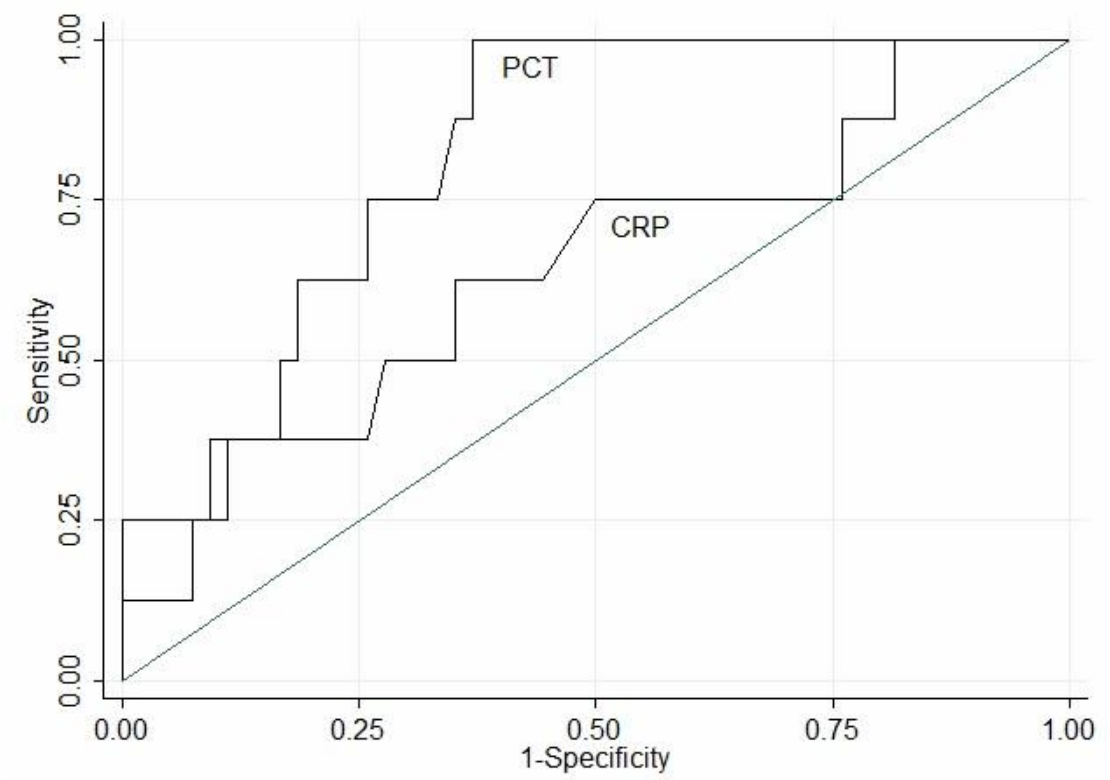

Figure 1: Receiver operator characteristic curves of PCT and CRP