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Interest of Serum Procalcitonin in the Diagnosis of Early Neonatal Bacterial Infections in Kisangani

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Abstract

Introduction: Blood culture remains the gold standard for the diagnosis of neonatal infections, however, it is not always available and even when it is accessible, obtaining the result requires 48 - 72 hours. For this, there is a need to use early, sensitive and specific biomarkers. This study aimed to evaluate the interest of procalcitonin in the diagnosis of Early Neonatal Bacterial Infection (INBP) in Kisangani in the Democratic Republic of the Congo (DRC). **Methods**: This was a cross-sectional descriptive study conducted from June 28, 2023 to January 15, 2024. A blood culture sample and procalcitonin assay were taken from any newborn suspected of INBP. The calculation of medians, percentages and statistical analyses of the characteristics of the test performance were carried out with R software version 4.4.2. **Results:** One hundred and twenty-three newborns suspected of INBP were divided into 3 groups, including 5 (4.1%) cases of definite infection with positive blood culture, 81 (65.8%) cases of probable infection with positive PCT and 37 (30.1%) cases without infection. The median PCT of the definite infection group was higher than that of the probable infection group. All 5 cases positive in blood culture also had positive PCT. The threshold of PCT positivity was 2.97 ng/ml, and the sensitivity and specificity were 80.0% and 67.8%, respectively. **Conclusion:** PCT has been shown to be useful in contributing to the diagnosis of INBP. It could help with the early establishment of INB in our setting and thus facilitate early management.

Keywords

Procalcitonin, Early Neonatal Bacterial Infection, Kisangani

1. Introduction

Early Neonatal Bacterial Infection (INBP) refers to an infection occurring within the first 72 hours after birth [1]. It is a neonatal infection transmitted from the mother to her newborn. It remains a leading preventable cause of neonatal morbidity and mortality worldwide and is a challenge for the clinician [2]. The clinical signs of these INBPs are often subtle and nonspecific in the newborn [3]. According to the World Health Organization (WHO), neonatal infections are the third leading cause of death, after preterm births and complications of childbirth (birth asphyxia) in developing countries [4]. Their incidence is higher in developing countries than in industrialized countries [2].

Blood culture, which is the gold standard, is still not available. Apart from the fact that it could be compromised due to inadequate blood volume sampling in newborns, bacteriological confirmation is also lacking due to the great difficulty of isolating the germ in this category of infection [5] [6]. In developing countries, newborns suspected of infection are treated with empirical antibiotics. These antibiotics promote bacterial resistance to antibiotics, alter the gut microbiota, and increase the costs of care [7]. Some newborns may be completely asymptomatic in the early stages of infection. Therefore, such situations may lead to a delay in the treatment of infected newborns or treatment of uninfected cases, which is not without complications [8]. It is therefore necessary to improve diagnosis to better identify newborns requiring antibiotic therapy from those who do not [9].

In the absence of methods for detecting the bacterial pathogen, the diagnosis of INBP is based on clinical signs and an increase in the concentrations of biomarkers such as Procalcitonin (PCT) [10]. Several publications note the fact that PCT is more specific for bacterial infections and can help distinguish bacterial infections from viral diseases. In addition, it has favorable kinetics for use as a clinical marker because it increases rapidly within 6 to 12 hours following stimulation [11]. According to studies, PCT would be an early marker of neonatal infection. It must be said that most of the studies that have demonstrated this have been carried out in developed countries [12]. In Sub-Saharan Africa (SSA), similar studies are almost non-existent. In the Democratic Republic of the Congo (DRC), to our knowledge, there are no studies that have addressed this topic. In Kisangani, one of the main cities of the DRC, a study evaluated the interest of CRP in the diagnosis of bacterial infection [13], but no study has been carried out on PCT, hence the need to conduct this study whose aim is to evaluate the interest of PCT in the diagnosis of INBP in Kisangani.

2. Materials and Methods

2.1. Study Framework

This was a cross-sectional descriptive study conducted during the period from June 28, 2023 to January 15, 2024 in the city of Kisangani, capital of the Tshopo Province in the North-East region of the DRC. Six health care Establishments (ESSs) caring for children and all belonging to the bacteremia surveillance network were

selected. Five of these ESS are public state facilities (Department of Pediatrics of University Clinics, General Reference Hospital of Kabondo, Makiso-Kisangani, Cinquantenaire Hospital, ALABUL Health Center) and only one ESS in particular, the New Village Pediatric Hospital Center, is a private facility.

2.2. Population and Sample

The study population consisted of all newborns born during the period of our study. We used exhaustive sampling, resulting in a sample of newborns suspected of infection, aged less than 72 hours. Newborns with risk factors for INBP and clinical signs of infection were included in the study. According to the criteria of the National Agency for Accreditation and Health Evaluation (ANAES) [14]. Newborns with multiple malformations, or who had previously received antibiotics before transferring to the selected ESS and those whose parents had not consented to the study were excluded.

2.3. Data Collection Technique

Using a pre-established form, we prospectively collected sociodemographic data from newborns (age and sex) and their mothers (age, municipality of residence, level of education, marital status, occupation, prenatal consultation follow-up, mode of delivery) as well as clinical data from newborns (Apgar at 5th minute, risk factors for infection, birth weight, head circumference, size, symptoms and management data) of newborns. They were examined by trained physicians who were able to diagnose suspected INBP. A 1 - 2 ml blood sample was taken using a clean vacutainer tube and sent to the laboratory for PCT assay and blood culture.

2.4. Test Procedure

All blood for both analyses was obtained in a single sample.

2.4.1. PCT Dosage

Assay was performed on the blood samples of the newborns by a trained laboratory technician according to the standard operating procedure of the test (Fluore Care PCT Kit, China). This is a test diagnostic immunochromatographic assay used to detect the concentration of PCT in serum by the double antibody sandwich method. The technique consisted of collecting one-half to one milliliter of blood in a clean, dry, impermeable vacutainer tube and transporting it to the laboratory. After centrifugation at 2500 rpm, 20 µL of blood sample was added to the 180 µL diluent solution tube and mixed for 2 minutes. Seventy microliters of this mixture were applied to the card, which was to be placed at room temperature for 15 minutes before inserting it into the test card holder of the analyzer. A few seconds later, the result was automatically displayed on the screen. The reference range of the diagnostic kit for PCT was 0.5 ng/ml.

2.4.2. Procedure and Analysis of Blood Cultures

For blood culture, neonatal blood samples (1 - 2 ml) were collected by aseptic pe-

ripheral venipuncture [15].

Neonatal blood samples were added to pediatric blood culture bottles of the BACT/ALERT * FP Bio Mérieux type; after that, the bottle was kept at room temperature. The transport of blood culture bottles was done at room temperature, from the sampling site to the laboratory of the pediatric department of the university clinics of Kisangani in a "Bac".

Culture was performed after incubation for a maximum of 7 days, positive bottles (having turned) were inoculated on two Petri dishes, one made of fresh blood agar (GSF) and the other made of Mac Conkey medium (PVX) after direct examination and Gram staining. Gram positives were isolated on GSF and Salt Agar Medium (MSA), while Gram negatives were isolated on GSF and Mac Conkey.

The identification of bacteria was carried out 24 to 48 hours later, by comparing the different biochemical characteristics of the Api galleries. We considered the following germs as contaminants: *Bacillus* spp., *Micrococcus* spp. and Coagulase-Negative Staphylococci (CNS). The test result was recorded in the patient record and communicated to the mother as part of the child's care.

INBP was defined as an infection occurring within the first 72 hours of life [16]. The newborn suspected of neonatal infection is one presenting an antenatal risk factor or a clinical sign.

2.5. Statistical Analyses

The study data were recorded on Epi Info version 7.2.2.6 and the statistical analysis was performed with R software version 4.4.2. Categorical data are described by numbers and percentages, while quantitative data are presented with regard to their statistical distribution in terms of median and interquartile range. Comparisons between groups (in particular the certain infections/probable infections/no infections groups) for categorical data were performed by the Fisher exact test and comparisons for quantitative variables were performed by the Kruskal-Wallis test. These analyses were completed in a second step by a ROC curve approach for which the results were expressed in terms of AUC and 95% confidence interval. The analysis of the ROC curve characteristics was performed by evaluating the area under the curve, the sensitivity and the specificity of PCT, considering blood culture as the reference examination.

2.6. Ethical Consideration

The study protocol was approved by the ethics committee of the University of Kisangani (N˚UNIKIS/CER/015/2023). We also obtained authorization from the administration of each ESS. Written or oral informed consent was obtained from each mother before including the newborn in the study.

3. Results

A total of 123 newborns were divided into 3 groups, respectively of 5 certain infections, 81 probable infections and 37 no infections.

The median PCT in the definite infection group was higher 5.7 [3.1 - 9.4] than in the probable infection group 2.8 [1.0 - 19.1] with a significant difference (Table 1). The threshold for PCT positivity was 2.97 ng/ml with a sensitivity and specificity of 80.0 % and 67.8 %, respectively (Table 2). The ROC curve of PCT shows that the Area under the Curve (AUC) is 0.74 (Figure 1).

The blood culture performed confirmed the infection of five newborns (4.1%): two had positive blood cultures for *Enterobacter* spp., two others for *Staphylococcus* spp. and one for *Serratia* spp.

Table 1. PCT variations according to blood culture results and group distribution for newborns.

Variables	Certain infection N = 5[1]	Probable infection N = 81[1]	No infection N = 37[1]	Total N = 123[1]	p-value
PCT (ng/ml)	5.7 [3.1 - 9.4]	2.8 [1.0 - 19.1]	0.3 [0.2 - 0.4]	1.3 [0.4 - 6.6]	**<0.0001[2]**
PCT					**<0.0001[3]**
Positive	5 (100.0%)	81 (100.0%)	0 (0.0%)	86 (69.9%)	
Negative	0 (0.0%)	0 (0.0%)	37 (100.0%)	37 (30.1%)	
Blood culture					**<0.0001[3]**
Positive	5 (100.0%)	0 (0.0%)	0 (0.0%)	5 (4.1%)	
Negative	0 (0.0%)	81 (100.0%)	37 (100.0%)	118 (95.9%)	

[1]Median [EI], n (%); [2]Kruskal-Wallis test; [3]Fisher's exact test.

Table 2. Sensitivity and specificity of procalcitonin.

Variables	Sensitivity (CI)	Specificity (CI)
PCT (2.97 ng/ml)	80.00 (28.4 - 99.5)	67.80 (58.6 - 76.1)

CI = 95% Confidence Interval.

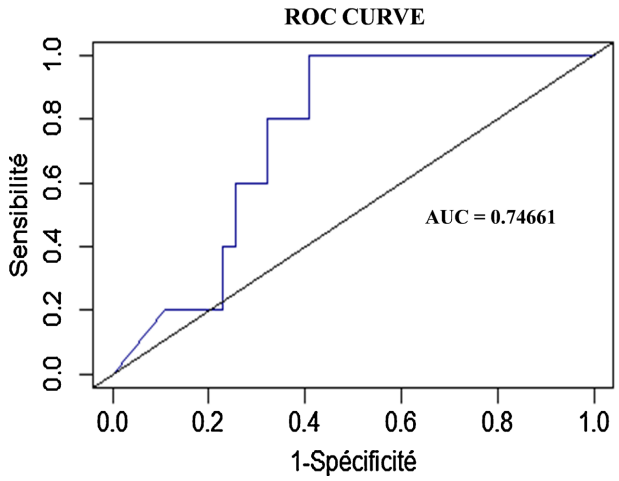

Figure 1. ROC curve characteristics of procalcitonin.

4. Discussion

INBP remains a concern for clinicians in low-income countries, especially in Sub-Saharan Africa, because of its difficult diagnosis and non-specific symptoms. This study aimed to assess the value of serum PCT in Kisangani hospitals. Indeed, PCT has been reported as a sensitive marker for early diagnosis. After injection of endotoxin, its concentration increases and is detectable after four hours and then reaches a peak after six to twelve hours [17]. In our study, the median PCT of the certain infection group was significantly higher than that of the probable infection group (5.7 ng/ml versus 2.8 ng/ml). PCT concentrations were found to be variable, although most values were between 0.4 and 6.6 ng/ml. These concentrations vary according to the studies, depending on the gestational age and the mode of delivery [3].

In our study, the optimal cutoff value was 2.98 ng/ml with a sensitivity and specificity of 80.0 % and 67.80%, respectively. This result is similar to that found in Cameroon by Alima Yanda *et al.* [12]. PCT has a high sensitivity in bacterial infections, which would make it an ideal biomarker for INBP. The PCT threshold varies among studies depending on factors such as the incidence of early neonatal infection, the endpoints, and the study population [17]. PCT can be used as an important index for diagnosis and treatment evaluation in neonates with systemic bacterial infection [16]. Our result also corroborates that found by Maamouri *et al.* in Iran with high sensitivity and specificity [18]. Our study showed that the area under the curve AUC was 0.74, which demonstrates a good ability of the test to discriminate infected and sick neonates from those who are not infected. In a recent meta-analysis, PCT had a good discriminatory value for neonatal sepsis in low-income countries [19]. It is a reliable approach that can improve the quality of care and enable rational use of antibiotics in settings where access to reference diagnosis is limited.

5. Conclusion

PCT showed good performance in contributing to the diagnosis of INBP in Kisangani, a resource-limited setting. It was positive in all 5 cases of definite infections confirmed by blood culture. In resource-limited countries where blood culture is still not available, it can be used as a reliable marker for early identification of infected newborns.

6. Limitations of the Study

We were unable to perform serial dosing. Also, the results were not correlated with gestational age and birth weight. Therefore, case-control studies on a large cohort of newborns should be conducted.

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Authors' Contributions

The design of the protocol was provided by HMV, and the clinical examination of newborns suspected of INBP and the data collection were provided by the following authors: HMV, VMK, and DGM. The correction of the study protocol and the manuscript were provided by DFS, ETK and JPAO. All authors read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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