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"Rule Out" Neonatal Sepsis: The Frequency of Early-Neonatal Infection in Late- Preterm Neonates Related to Maternal Risk Factors

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Abstract: ***Introduction****: Sepsis has always been one of the most common complications affecting newborn infants with a high rate of mortality and morbidity during neonatal period. Starting early antibiotic therapy is crucial for treatment success. But incidence of sepsis, in neonate treated for suspected sepsis, is low, exposing in this case not necessary of this babies to antibiotics with all of sides effects(high rate of late sepsis, mortality, and high cost).* ***Purpose****: To evaluate the most sensitive marker in early diagnosis of neonatal sepsis or rule out early neonatal sepsis in suspected early-onset sepsis neonates (EOS).* ***Material and Methods****: This single-center, prospective, randomized intervention study conducted in a tertiary neonatal intensive care unit, janary 2011-december 2014. All neonate with suspected sepsis were randomly assigned either to standard treatment based on conventional laboratory parameters (standard group) or to PCT-guided treatment (PCT group). Minimum duration of antibiotic therapy was 72-96 h in the standard group, whereas in the PCT group antibiotic therapy was discontinued when two consecutive PCT values were below predefined age-adjusted cut-off values(<2 ng/ml).* ***Results****: 340 newborns were randomly assigned wither to the standard group (n = 187) or the PCT group (n = 153). The two groups were similar for baseline demographics, risk factors for EOS, gestational age, birth weight, Apgar score 1 and 5 minute, and early conventional laboratory findings (CRP, WBC, I/T index, PLT). PCT show to be more sensitive related to other markers, sensitivity was 90.9% and NPV 96.15%.There was a significant difference in the proportion of newborns treated with antibiotics 72 h between the standard group (85.29%) and the PCT group (59%) (ARR 26.3%; odds ratio 0.2 (95% CI 0.07-0.7), p = 0.019). When sepsis rule out, we found significance difference between two groups in antibiotics use ≥72h , standart group 80% vs 45.45 % PCT group(odds ratio 9.5(95% CI 1.7-52). No difference beetwen two groups in GA <34 weeks. In this cases duration of antibioticotherapi ≥72h was for noninfective risk, but for neonatal risk. On average, PCT-guided decision-making resulted in a shortening of 40 h of antibiotic therapy in GA >34 weeks neonates. No difference found in antibiotics treatment in neonates with sepsis in two groups. Clinical outcome was better in study group related to secondary sepsis episode. Conclusion: PCT kit test show to be useful to rule-out early neonatal sepsis. Also seem to be useful in shorten the duration of antibiotic therapy in near-term infants with suspected early-onset sepsis, but our data are insufficient , and before this PCT-guided strategy can be recommended in our practice , its safety has to be confirmed in a larger number of neonates.***

Keywords: neonatal sepsis, PCT, sensitivity, NPV, antibiotics.

1. Introduction

Sepsis has always been one of the most common complications affecting newborn infants. It is normally divided into three categories, depending on time of onset: early onset sepsis (EOS) at ≤ 3 days of age, late onset sepsis (LOS) at 3-28 days of age, and late late onset sepsis (LLOS) at 29-120 days of age. Of these, LOS is the most common infection, especially in very low birth weight (VLBW) infants. The reported incidence of sepsis varies between 1 and 10 per 1000 live births, but large population-based studies are few, and most of the studies available are focused on high-risk infants such as premature or VLBW children[7-14]. It is even harder to assess the incidence of neonatal sepsis in the developing countries , but rates between 2 and 50 per 1000 live births have been reported for early onset sepsis. High levels of mortality, nonspecific clinic, low sensitivity and sensibility of diagnostic tests and incomplete data about prenatal risk factors are causes of why we start antibiotic therapy in suspected cases, without confirmation of laboratory tests, specially of blood culture. That-s why antibiotics are the most abused medicaments in NICU, despite strict protocols of their use. This is the main reason antibiotic resistance, high costs of neonatal care and longer stay of newborns in NICU. For this reason we need an biological marker with high sensitivity and high NPV(negative predictive value) that rule-out early neonatal sepsis. For several years are proved different markers but the interest is focused in sensitive markers as interleukins and procalcitonine. Both have shown to be infection marker not inflammation markers and procalcitonine show to be longer in blood and easily measured. The purpose of this study is to show the usefulness of semi quantitative PCT_Q kit test in the early diagnose of neonatal sepsis evaluating his sensitivity, sensibility and negative predictive value (NPV) compared with other markers used in the diagnose.

2. Material and Methods

This single-center, prospective, randomized intervention study conducted in a tertiary neonatal intensive care unit, janary 2011-december 2014.There are included in the study 340 newborns suspected of infection, separated in two groups: 1-standart group (n-187) diagnose based in actual protocol of clinic (CRP, WBC, I/T index, PLT, blood culture); 2-PCT group (n-153) – Diagnose based on conventional laboratory parameters and PCT (Antibiotic therapy was discontinued when two consecutive PCT values were below predefined age-adjusted cut-off values(<2 ng/ml).

There are excluded newborn with congenital anomaly and metabolic disease.
Patients are divided in four clinical groups: S1- confirmed sepsis; S2- clinic sepsis; S3- suspected sepsis; S4 – no sepsis.

Other data and laboratory tests
analyzed all neonatal and maternal risk factors as maternal IUV, fever, PPROM, Chorioamnionits, antenatal antibiotics use from mother, preterm delivery, perinatal asphyxia, other maternal illness and perinatal events like use of oxytocin, distress fetal etc. We also analyzed clinical signs in the newborns suspected for neonatal sepsis.

Blood culture was realized in HEMOLINE (DIPH-F) bottle. We have considered as significant values of sepsis: leucocytes < 5000 or >20000 mm^3; I/T > 0.2 and thrombocytes < 100 000 mm^3. Because of limited financial sources we evaluated CRP with semi-quantitative and qualitative method. All suspected babies for sepsis have been treated with antibiotics.
Statistical analysis
We evaluated sensitivity, specificity, PPV, NPV for all diagnostic tests that we used (WBC, I/T, PLT, CRP, PCT), and also OR for CI 95%. We used Fisher test to compare groups and Mann-Whitney U test for variables.

3. Results

We analised 374 still borns GA>32 weeks suspected for sepsis, with maternal risk factors as maternal fever >38^{0}C, maternal not treated urinary infection, Chorioamnionitis, prematur labor etc) and/or in presence of clinical signs of neonatal sepsis when empirical started of antibioticotherapie is needed. Study duration January 2011-December 2014 in "Koco Gliozheni" Maternity Tirane Albania.

34 cases were excluded for congenital anomaly or incomplet data. 340 babies incluted in our study were divided acording study`s criterias in two groups: 153 patients= PCT study group and the control group of 187 patients was conducted according a standard protocol of sepsis diagnosis and clinical treatment.

Both groups proved equal to key demographics data such as gestational age, birth weight, Apgar Score at minutes I and V, sex, route of birth, prenatal use of antibiotics, but uneven in terms of risk factors, the manner of birth and incidence of infection. (See table 1)

Table 1: Demografics Data

	PCT(N=153) Study group	Control group(N =187)	P<0.5
GA	33.7±2.64	33.8±2.69	p=0.19
Birth weight	2061.57±86.6	2100±73.8	P=0.43
Apgar I V	7.38±1.63 8.53±1.06	7.45±1.63 8.6±1.04	P=0.23 P=0.08
Spontaneus Vaginal delivery S/C Induction	82/153 71/153 24/153	108/187 79/187 70/187	p=0.14 p=0.04 p<0.001
Male Female	91/153 62/153	71/187 117/187	p=0.2 p=0.22
Not risk factor	81/153	66/187	P=0.001
PROM>18 h	57/153	91/187	P=0.03
Chorioamnionitis	7/153	12/187	p=0.46
Intrapartum antibiotics	29/56	36/106	p=0.02
Antibiotics & risk factor	56/61	106/108	P=0.056
S1+S2	10/153	27/187	p=0.01
S3	85/153	96/187	p=0.5
S4	58/153	64/187	p=0.4

Groups were compared for all hematological tests used and resulted in no significant change to the leukocyte and platelet number. Both of them resulting to be more sensitive to the late sepsis diagnosis.While the index in terms of I / T, bands and CRP difference was significant. (See Table 2)

Table 2: Assessment of probability of infection and early convencional laboratory findings

	PCT group (n=153)	Standart group (n=187)	P value
WBC= 12h (10^3) mean	16.9(4.9-41)	17.6(3.1-3.5)	0.9
WBC= 36h (10^3)mean	17.1(6.1-35)	(15.9-41.7)	0.13
I/T ratio >0.2 12 h	63	40	0.02
I/T ratio >0.2 36h	43	40	0.24
Bands >10% 12h	63	40	0.02
Bands >10% 36h	21	20	0.16
PLT 12 h mean	235(89-473)	243(102-385)	0.23
PLT 36 h mean	247(94-487)	262(103-384)	0.16
CRP (poz) 12h	68/153	126/187	0.002
CRP (poz) 36h	69/153	113/187	0.003
S1+S2	10/153	27/187	p=0.01
S3	85/153	96/187	p=0.5
S4	58/153	64/187	p=0.4

The processing and analysis of data showed no significant difference in the diagnosis, in real cases with sepsis. Interesting was the fact that the time of diagnosis of sepsis exemption in cases where sepsis was unlikely, and diagnosis time was reduced by approximately 2 days (See table 3)

Table 3: Diagnosis time

	PCT group	Standart group	CI 95%	P<0.05
S1+S2(days)	2.6±0.7	2.77±0.4	0.17(0.05-0.29)	0.39
S3	2.9±0.19	4.25±0.28	1.35(1.3-1.4)	0.0001
S4	2.36±0.13	4.2±0.2	1.84(1.8-2.88)	<0001

6. Discussion

In this prospective intervention study, we were able to show that PCT-guided decision –making reduced the time of sepsis diagnosis and duration of empirical antibioticotherapi in neonates suspected for sepsis. The gold standart for diagnosis of neonatal sepsis is blood culture, but is often unreliable because of frequent use of intrapartum antibiotics or insufficient amounts of blood for culture. So use of PCT measurements allow shortenig diagnosis time. But we need large studies to test reliability and safety of a PCT-based strategy.

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