

Role of Semi Quantitative Procalcitonin Test-Kit in Early Detection of Neonatal Sepsis and in Antibiotics use Reduction

Niketa Koliqi¹, Eli Foto², Eduard Tushe³

¹Neonatal Intensive Care Unit, UOGH "Koço Gliozheni" Tirana Albania

²Professor, Head of Pediatric Infection Disease Departement , UHC "Mother Tereza" Tirana , Albania

³Professor, Head of Neonatal Intensive Care Unit, UOGH "Koço Gliozheni" Tirana Albania

Abstract: ***Background:** Clinical signs and laboratory tests of neonatal sepsis are non-specific and diagnosis is difficult. Confirmation of diagnosis needs time. Laboratory tests used to diagnose neonatal sepsis are blood culture, bloodcount, I/T index and CRP which have low sensitivity and specificity. Last year studies show use of procalcitonin(PCT) as early biomarker of infection. **Purpose:** To evaluate and use the effect of procalcitonin (PCT) in diagnosis of neonatal sepsis and PCT-guided decision on duration of antibiotic therapy in suspected neonatal early-onset sepsis. **Objectives:**-Determination of sensitivity and specificity of PCT in the diagnose of neonatal sepsis (SEMI QUANTITATIVE PROCALCITONIN TEST- KIT method)-Negative predictive value of PCT in the diagnosis of neonatal sepsis-Reduction of antibiotic therapy use. **Material and Methods:** This single-center, prospective, randomized intervention study conducted in a tertiary neonatal intensive care unit, janary2012-december 2013, and is still in process. There are included in the study 148 newborns suspected of infection, separated in two groups:-PCT group (nr-78) – 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). -Standard group (n_70) -diagnose based on actual protocols of clinic. This study has evaluated sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) for all laboratory tests used in the diagnose of neonatal sepsis. **Results:** 148 newborns were randomly assigned wither to the standard group (n = 70) or the PCT group (n = 78). The two groups were similar for baseline demographics, risk factors for early-onset sepsis, gestational age, birth weight, Apgar score 1 and 5minute, prenatal risk factors and early conventional laboratory findings. 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%) (absolute risk reduction 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 ≥ 72 h , standart group 80% vs 45.45 % PCT group(odds ratio 9.5(95% CI 1.7-52). No difference between two groups in GA <34 weeks. In this cases duration of antibioticotherapi ≥ 72 h 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 babies. 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:** Use of PCT kit test show to be useful in early sepsis diagnosis. 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

Neonatal sepsis is a clinic syndrome which has signs and symptoms of infection with or without bacteremia in the first month of life. Diagnose is still difficult despite all achievements of lasts years in neonatology and neonatal sepsis is one of the most important causes of morbidity and mortality mainly in preterm babies.

Incidence of neonatal sepsis varies from 1-3/1000 alive newborns to 10-15/1000 live born babies and this risk increases to 4-10 times for babies weighing < 1500 gr.

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.

That-s why we need fast laboratory tests with high levels of sensitivity and sensibility as PCT. A lot of studies report the usefulness of SEMI QUANTITATIVE PROCALCITONIN TEST- KIT method in the early diagnose of neonatal sepsis. Newborns that suffer viral infections, early neonatal sepsisor respiratory detres from other reasons has normal or moderate levels of PCT.

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, January 2012-December 2013, and is still in process. There are included in the study 148 newborns suspected of infection, separated in two groups:

- PCT group (n_78) – 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).
- Standard group (n_70) -diagnose based on actual protocols of clinic.

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

Table 1: Diagnostic criteria

S4 (No sepsis)	Presence of ONE criteria below : <ul style="list-style-type: none"> • Maternal/ perinatal risk factors • Clinical signs of sepsis • Laboratoric findings.
S3(Suspected Sepsis)	Presence of TWO criteria below : <ul style="list-style-type: none"> • Maternal/ perinatal risk factors • Clinical signs of sepsis • Laboratoric findings.
S2(Clinical Sepsis)	Presence of THREE criterias below : <ul style="list-style-type: none"> • Maternal/ perinatal risk factors • Clinical signs of sepsis • Laboratoric findings.
S1 (Confirmed Sepsis)	≥1 data (Maternal/ perinatal risk factors, Clinical signs of sepsis Laboratory findings.) AND POSITIVE blood culture.

* see tab. 2

Tab. 2

<i>Maternal/ perinatal risk factors</i>	Mother GBS positive PROM>18 h Chorioamnionitis (temp.>38.5°C, distress fetalis GA <35w IVU no treated 2 last weeks
<i>Clinical signs of sepsis</i>	Respiratory signs (DR/apnoe) Cardiac rate >180/min <80/min Hypotension Instability of temperature Seizures/irritability/letargy/ Feeding problems, vomiting and gastric intolerance
<i>Laboratory findings</i>	WBC<5000/mm ³ or >20000/mm ³⁽⁵⁾ , I/T >0, 2 PLT<100, 000/mm ^{3(5, 6)} PCR pozitiv Hemokulturë pozitiv

Other data and laboratory tests

We analyzed all neonatal and maternal risk factors as maternal IUV, fever, PPROM, chorioamnionitis, antenatal antibiotics use from mother, preterm delivery, perinatal asphyxia, other maternal illness and perinatal events like use of oxytocin, distress fetalis 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 mm³; I/T > 0.2 and thrombocytes < 100 000 mm³. 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

From January 2012-December 2013 we analyzed 148 newborns were randomly assigned wither to the standard group (n = 70) or the PCT group (n = 78) with the characteristics as below:

Table 3: Characteristics of patients

	PCTgroup (N=78)	Standard group(N =70)	p
MB	33.7±2.64	33.8±2.69	p=0.9
Weight	2061.57±630	2100±664.8	P=0.97
Apgar I	7.38±1.63	7.45±1.63	P=0.91
V	8.53±1.06	8.6±1.04	P=0.91
Labour			
Vaginal	40/78	38/70	p=0.14
S/C	38/78	32/70	p=0.04
Sex			
Male	48/78	36/70	p=0.2
Female	30/78	34/70	p=0.22
No maternal risk factors	32/78	34/70	P=0.2
PROM>18 h	26/78	28/70	P=0.24
Chorioamnionitis	6/78	2/70	p=0.08
Antibiotics intrapartum	28/78	20/70	p=0.27
S1+S2	22/78	6/70	p=0.08
S3	12/78	12/70	p=0.3
S4	44/78	50/70	p=0.06

There were no differences between two groups for what concerns gestational age, weight, Apgar score, delivery and other characteristics. We have analyzed sensitivity, specificity, PPV, NPV for all diagnostic tests used.

Table 4

Diagnostic test	Sensitivity	Specificity	PPV	NPV
PCT	90.9	89.3	76.9	96.15
CRP	54.54	53.5	31.37	75
Leucocyte 12h	38.8	89.28	40	73.5
I/T 12h	27.78	60.71	21.4	68
Bands 12h	45.5	67.85	35.7	76
PLT 12h	52.7	67.85	47	86.3
Blood culture	27.27	85.7	42.8	75

According to our analysis result that PCT has better sensitivity and NPV than other tests (cut-off < 2ng/ml), the same specificity with leucocytes at 12h and blood culture.

At the PCT group antibiotic therapy has been stopped after 2 negative values of PCT < 2ng/ml. There was a significant difference between newborns treated with antibiotic over 72h, standard group (85.29%) and PCT group (59%) (absolute risk reduction 26.3%. OR 0.2; CI 95% (0.07-0.7) p=0.019). The impact of PCT in the reduce of antibiotic therapy depends on the probability of infection specially for patients classified as S3 and S4.

Table 5: Antibiotic therapy $\geq 72h$

	Standard group N=70	PCT group n=78	Absolute risk reduction (ARR)	p
Total	58/70 85.29%	26/78 59%	26.3%	0.019
S1+S2	6/6 100%	22/22 100%	0%	
S3	12/12 100%	4/12 33%	67%	0.01
S4	40/50 80%	20/44 45.45%	34.55%	<0.02

There is a reduction of 40h for antibiotics use, between standard group and PCT group, for S3 patients group.

Table 6: Reduction of duration of antibiotics

	Standard group N=70	(PCT group) n=78	Absolute reduction	p
Total (antibiotic hour)	193.2	110.2	83.4	0.012
S1+S2	268	270	2	0.8
S3	148	115.2	32.8	<0.002
S4	139.2	67.4	71.8	<0.001

Table 7: Reduction of duration of antibiotics MB>34W

	Standard group N=38	PCT group n=26	Absolute reduction
Total (antibiotic therapy hours)	143.4	99.69	43.7
S1+S2	240	230	10
S3	144	95.2	48.8
S4	88	48	40

4. Discussion

Despite high levels of sensitivity and specificity of some diagnostic markers, none of them alone can decide the diagnosis of neonatal sepsis. Results of literature and also findings of our study testify PCT test as the best to rule out the diagnosis of neonatal sepsis. These results can help also to reduce the duration of antibiotics. Our modest study show a reduction with 40h of antibiotic therapy for newborns less than 34 weeks, suspected for neonatal sepsis.

5. Conclusions

Use of PCT kit test show to be useful in early sepsis diagnosis. 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. The European and International Society for Sexual Medicine guidelines state that the inclusion criteria for studies on management of PE must ensure that participants have PE and no other sexual dysfunction, such as erectile dysfunction, and that the IELT measurement as a specific entry criterion is not a necessity. Finally, the inability to reach decisive clinical conclusions is derived from the lack of agreed -on definitions for PE and well- accepted outcome measures to monitor treatment efficacy. The lack of conclusive evidence emphasizes the need for a large population, randomized, double-blind, placebo-controlled study to assess the efficacy of PDE5-Is, SSRI alone, respectively or their combination in the management of PE.

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