COMPARISON BETWEEN PROCALCITONIN AND C-REACTIVE PROTEIN AS A SENSITIVE MARKER OF EARLY ONSET SEPSIS AMONG SAUDI NEONATES

By

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ABSTRACT

Background & objectives: *Early diagnosis of neonatal sepsis (NS) is difficult because of the variable and non-specific clinical presentation. Also, many laboratory tests are negative at the early stage of diseases, so the study aimed to detect the role of procalcitonin (PCT) in early detection of NS versus to C-reactive protein (CRP) and other hematological parameters.*

Methods: *A cross-sectional study was conducted on 150 newborn babies with signs suggesting sepsis admitted to neonatal intensive care units (NICU) at 2 (As-Salama and Alawi Tunsi) hospitals in KSA. Laboratory tests including PCT, CRP, complete blood count (CBC), erythrocyte sedimentation rate (ESR) and blood cultures were done for all cases.*

Results: *Based on clinical findings and laboratory data; 28%, 32% and 40% of patients were categorized as culture proven sepsis, suspected sepsis and clinical sepsis respectively. PCT was positive in 92.9%, 58.3% and 3.3% compared to CRP positivity in 50%, 43.8% and 20% of patients with proven sepsis, suspected sepsis and clinical sepsis respectively. PCT sensitivity, specificity, positive predictive value and negative predictive value were 92.8%, 72.2%, 59% and 96% respectively while CRP results were 50%, 69.4%, 38.8% and 78.1% respectively. Serum values of PCT and CRP differed significantly in the 3 sepsis groups indicating relation to the severity of sepsis. Altered hematological parameters founded only in 14.3% of proven sepsis cases.*

Conclusions: *Serum PCT level was superior to serum CRP level in terms of early diagnosis of NS and in detecting the severity of illness. and altered hematological parameters have a minor role for early detection of sepsis.*

Keywords: *C-reactive protein, Neonatal sepsis, procalcitonin.*

INTRODUCTION

Neonatal sepsis (NS) is defined as a systemic condition of bacterial, viral, or fungal origin which is associated with hemodynamic changes and other clinical manifestations and results in substantial morbidity and mortality **(Andi et al., 2017)**.

In the United States, the incidence of EOS with positive blood cultures is estimated to be 0.77 to 1 per 1,000 live births **(Stoll et al., 2011)**. In Egypt, a prevalence of 4.02/1,000 live births **(Seliem and Sultan, 2018)** and an incidence of 43.9% **(EL-Mashad et al., 2019)** were reported while in Saudi Arabia an incidence of 4.44/1,000 live births was reported by **Almudeer et al., (2020)**. The neonatal sepsis may be complicated with seizures, sensorineural hearing loss, visual disorders, neurodevelopmental defects, and even death. Those complications can be avoidable if NS treated early, however; the early signs and symptoms are often nonspecific and confusing which makes it difficult to establish an early clinical diagnosis, and so antibiotics are often started on the clinical suspicions of sepsis **(Alrafiaah et al., 2016)**. This approach is effective in fighting against the acute infections but increases the risks of antibiotics side effect and the emergence of drug resistant organisms in neonatal units **(Shriazi et al., 2010)**. The gold standard for diagnosis of sepsis is blood culture but it is time consuming up to 36 hours (24-72 hours), of incubation period, specificity 100% **(Edgar et al., 2010)**. Other markers as acute phase proteins, cytokines, cell surface antigens and bacterial genomes have been used, either alone or in combination, for early diagnosis of neonatal sepsis. Some of these markers are sensitive and specific, but expensive and impractical **(Alrafiaah et al., 2016)**. For that, early diagnosis of neonatal sepsis is still a great challenge. For that reason, our study was conducted to assess the reliability of procalcitonin (PCT) as an early sensitive sepsis marker. The ideal diagnostic test should have quick results, with adequate sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to reliably exclude sepsis and avoid unnecessary antibiotic therapy. C-reactive protein (CRP) is an acute phase reactant synthesized by the liver and elevated in infection, auto immune diseases, surgery, meconium aspiration and recent vaccination. Also, the CRP values don't rise significantly until almost 24-48 hours after onset of infection and can't be used to

differentiate between bacterial and other infections **(Mishra et al., 2006)**. Also, CRP does not differentiate between systemic inflammatory response and sepsis **(Machado et al., 2014)**. Recently, Procalcitonin (PCT) was demonstrated to be an accurate biomarker for the diagnosis of sepsis in adults and showed to be promising in paediatrics **(Pontrelli et al., 2017)**. PCT is the precursor of calcitonin with no hormonal activity. It is a 116-amino acid peptide synthesized in the C cells of the thyroid gland. In healthy persons, PCT levels are undetectably low but in severe bacterial, fungal and parasitic infections with systemic manifestations, a significant rise in PCT levels are seen that is produced by extra thyroid tissue **(Kaur et al., 2013)**. Many studies have been conducted on the beneficial value of the quantitative measurement of PCT for an early detection of NS. The rise of PCT levels occurs before any observable rise in CRP concentrations **(Whicher et al., 2001)**. Other tests were usually used for the diagnosis of NS including CBC for leucocytic parameters, Platelets count and ESR **(Adib et al., 2012)**.

AIM OF THE STUDY

Our study aimed to determine the diagnostic performance of PCT and compare the PCT with CRP and other hematological parameters for early detection of neonatal sepsis.

Ethical consideration:

1. Consent was taken from the parents/care-givers. To participate in the study.
2. Approval of ethical committee in the Department College and university were obtained before the study.
3. No conflict of interest and fund from any source.
4. The results of the study were confidential.
5. The patient has the right to withdraw from the study.
6. The authors declared that there was no financial support regarding the study or publications.

Sample size:

Our sample study was calculated using the G*power software (version 3.1.9.2) computer program to reduce a type II error and increase the power, based on a chi-square (X2) test with comparison of the 3 studied groups. A minimum sample size of 143 neonates was

calculated considering a significance level of 0.05, medium effect size of 0.30, a power $(1 - \beta)$ of 0.80, and α was set a priori at 0.05. The sample size was set as 150 neonates.

Study Procedure:

A hospital based cross-sectional study was conducted on 150 neonates with suspected sepsis who were admitted to the neonatal intensive care unit (NICU) in As-Salama and Alawi Tunsi Hospitals in KSA during the period from April 2016 to April 2017. They were selected by simple random method.

Inclusion criteria:

1. Any suspected case of neonatal sepsis with maternal risk factors for sepsis e.g.:
    a. Premature rupture of membrane (PROM) > 18 hours,
    b. Maternal intrapartum fever,
    c. Maternal urinary tract infection,
    d. Chorioamnionitis.
2. Sepsis related clinical signs as temperature instability, apnea need for supplemental oxygen, tachypnea, tachycardia, feeding intolerance, abdominal distension and hypoperfusion.

Exclusion criteria:

Any newborn with history suggestive of:

1. Birth asphyxia,
2. Hyaline membrane disease,
3. Aspiration syndromes,
4. Inborn errors of metabolism
5. Infant of diabetic mother,
6. Congenital anomalies including congenital heart disease,
7. Severely jaundiced babies due to blood group incompatibilities.

Specimens and Tests:

Under complete aseptic conditions, 3 blood samples were obtained from each neonate prior to onset of antibiotics (by peripheral venipuncture). The 1st sample (0.5–1.0 mL) was collected in non-silicone coated vacutainer tubes containing heparin or EDTA. Work–up involved CBC along with hematological score system of **(Rodwell et al., 1988)** (HSS) **(Table 1)**. Blood smears were prepared, stained with Leishman stain and examined under oil-immersion lens at a magnification X1000. Hematological parameters were obtained by using automated Cell Dyn machine Corrected for nucleated red blood cells

(NRBCs). Differential leucocytic count (DLC) was performed on these smears. Blood culture was taken as a standard indicator for septicemia. All peripheral blood smears were analyzed, and by using HSS of Rodwell as shown in **Table (1)**.

Table (1): Hematological scoring system (Rodwell et al., 1988)

Criteria	Abnormality	Score
Total WBC count	≤5, 000/μl ≥ 25, 000 at birth ≥ 30, 000- 12-24 h ≥ 21, 000-Day 2 onwards	 1 1
Total PMN	No mature PMN Increased/decreased	2 1
Immature PMN count	Increased	1
I: T PMN ratio	Increased	1
I: M PMN ration	≥ 0.3	1
Degenerative changes in PMN	Toxic granules/cytoplasmic vacuoles	1
Platelet count	≤ 150, 000/ μl	1

HSS was scored in all cases of NS. HSS assigns a score of 1 for each of seven findings significantly associated with sepsis. Score of ≤ 2 was interpreted as sepsis unlikely; score 3-4: sepsis is possible and ≥ 5 sepsis or infection is very likely **(Rodwell et al., 1988)**.

Blood culture procedure:

The second blood sample for blood culture of at least 0.5-1 mL of blood was injected into standard blood culture bottle, labeled and sent to the laboratory. Cultures are incubated for 14 days. If growth is detected, bottles are sub cultured and antibiotic sensitivity test is carried out. Third serum sample of 1.0 mL was taken from each neonate for measuring the levels of CRP and PCT.

Serum CRP:

CRP was measured using CRP Kit (Ortho Clinical Diagnostic Vitros clinical chemistry slide) which is supplied in cartilages. The quantitative measurement of CRP from the serum was done by colorimetric, potentio-metric that utilizes dry slide technology. This method was done according to the manufacturer's instructions. The CRP reagent was linear up to 150 mg/L. The reference value was up to 6 mg/L **(Collaborators, 2016)**.

Serum PCT:

PCT level was measured by using a quantitative immuno-luminometry method and Lumitest kit (BRAHMS Diagnostic, Berlin, Germany). In this assay, a PCT level of ≥0.5 ng/ml was considered as pathological (Cotton, 2016). PCT levels of 0.5–2 ng/ml, 2–10 ng/ml and >10 ng/ml were considered as weakly positive, positive and strongly positive respectively.

Statistical analysis:

Data were analyzed using the SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). For descriptive statistics, the number and percentage were used for qualitative variables while mean ± SD were used for quantitative variables. In order to assess differences in frequency of qualitative variables, Chi square test or Fisher exact test (FET) were used while Independent samples t test was used to assess differences in quantitative variables. The sensitivity, specificity, PPV and NPV of the PCT and CRP for diagnosing sepsis were calculated. The statistical methods were verified, assuming a significant level of $p< 0.05$ and a highly significant level of $p<0.001$.

RESULTS

A total of 150 newborns, 53.3% males, 46.7% females, 84 preterm and 66 term, fulfilled the inclusion criteria. Based on clinical data and laboratory results including the clinical signs of sepsis, hematological scoring system and blood culture, the studied neonates were classified into 3 groups; Group–I, n=42 cases (28%) (proven sepsis) diagnosed by clinical signs and positive bacterial culture;

Group–II, n=48 cases (32%) (suspected sepsis) defined by clinical signs, negative bacterial culture and at least 3 or more positive screening tests i.e., HSS ≥ 3;

Group–III, n=60 cases (40%) (clinical sepsis) known by clinical signs of sepsis with negative bacterial culture and ± HSS ≤ 2.

Proven sepsis group was used as the gold standard for sepsis detection where PCT, CRP and other hematological parameters were correlated to this group regarding sensitivity, specificity, PPV and NPV.

Table (2): Organisms isolated in blood culture in Group–I

Organisms	n=42	%
Acinetobacter	15	35.7
Klebsiella pneumoniae	6	14.3
Staphylococcus aureus	6	14.3
Coagulase negative staphylococci (CONS)	6	14.3
Klebsiella Oxytoca	3	7.1
Citrobacter koseri	3	7.1
Pseudomonas aeruginosa	3	7.1

This table shows that the common culture-isolated organisms were acinetobacter (15/42), followed by klebsiella pneumoniae (6/42), staphylococcus aureus (6/42), coagulase negative staphylococci (CONS) (6/42), klebsiella oxytoca (3/42), citrobacter koseri (3/42) and pseudomonas aeruginosa (3/42).

Table (3): Comparison between laboratory findings in the studied groups

Variables		Proven sepsis n=42 (%)	Suspected sepsis n=48 (%)	Clinical sepsis n=60 (%)	All sepsis groups n=150 (%)	P-value
CRP	+ ve (> 6 mg/L)	21 (50.0)	21 (43.8)	12 (20.0)	54 (36.0)	**0.003***
	-ve (< 6 mg/L)	21 (50.0)	27 (56.2)	48 (80.0)	96 (64.0)	
PCT	+ ve (> 0.5 ng/mL)	39 (92.9)	28 (58.3)	2 (3.3)	69 (46.0)	**<0.001***
	-ve (< 0.5 ng/mL)	3 (7.1)	20 (41.7)	58 (96.7)	81 (54.0)	
Blood culture	+ ve	42 (100.0)	0 (0.0)	0 (0.0)	42 (28.0)	**<0.001***
	-ve	0 (0.0)	48 (100.0)	60 (100.0)	108 (72.0)	
Abnormal TLC	+ ve	6 (14.3)	18 (37.5)	6 (10.0)	30 (20.0)	**0.001***
	-ve	36 (85.7)	30 (62.5)	54 (90.0)	120 (80.0)	
High micro ESR > 10	+ ve	3 (7.1)	30 (62.5)	21 (35.0)	54 (36.0)	**<0.001***
	-ve	39 (92.9)	18 (37.5)	39 (65.0)	96 (64.0)	
Abnormal I/T ratio >0.2	+ ve	6 (14.3)	27 (56.3)	12 (20.0)	45 (30.0)	**<0.001***
	-ve	36 (85.7)	21 (43.7)	48 (80.0)	105 (70.0)	

Values present as number and % were analyzed by Chi-square test. *: Significant.

This table shows significant difference between the three studied groups regarding all the laboratory findings mentioned in the table where an elevated CRP level > 6 mg/L, an elevated serum PCT level > 0.5 ng/mL, and positive blood culture were significantly higher in proven sepsis group (50%, 92.9%, and

100% respectively). Abnormal TLC, high ESR, and abnormal I/T ratio were noticed in 14.3%, 7.1% and 14.3% of proven sepsis group respectively however, they were significantly lower when compared to similar findings in the suspected sepsis group.

Table (4): Comparison of serum PCT levels between the 3 studied groups

PCT	Proven sepsis n=42 (%)	Suspected sepsis n=48 (%)	Clinical sepsis n=60 (%)	P-value
Negative (< 0.5 ng/ml)	3 (7.1)	20 (41.7)	58 (96.7)	<0.001*
Weak positive (0.5 – 2 ng/ml)	0 (0.0)	12 (25.0)	1 (1.7)	<0.001*
Positive (> 2 – 10 ng/ml)	9 (21.4)	10 (20.8)	1 (1.7)	0.003*
Strong positive (> 10 ng/ml)	30 (71.4)	6 (12.5)	0 (0.0)	<0.001*

Values present as number and % were analyzed by Chi-square test. *: Significant.

This table shows that PCT level was related to the severity of infection as PCT showed significant strong positive values in most cases of proven sepsis (30/42, 71.4%) compared to other groups while negative PCT values were significantly obvious among clinical sepsis group (58/60, 96.7%). Positive PCT values were significantly higher in both proven and suspected sepsis groups when compared to that of clinical sepsis group while weak positive values were significantly higher among suspected sepsis group when compared other groups.

Table (5): The mean CRP and PCT levels in sepsis groups

Character	Proven sepsis	Suspected sepsis	Clinical sepsis	P-value
CRP (mean ± SD) mg/L	24.36 ± 33.8	10.21 ± 14.60	5.23 ± 2.66	0.010*[1]
				<0.001*[2]
				0.011*[3]
PCT (mean ± SD) ng/ml	6.70 ± 7.66	4.10 ± 4.38	0.50 ± 0.62	0.048*[1]
				<0.001*[2]
				<0.001*[3]

Values present as mean ± SD were analyzed by Independent samples t-test. *: Significant.
1: Difference between proven and suspected sepsis groups.
2: Difference between proven and clinical sepsis groups.
3: Difference between suspected and clinical sepsis groups.

This table shows statistically significant differences between the mean CRP and PCT levels between all groups. The mean values were significantly higher in proven sepsis group.

Table (6): Comparison between CRP and PCT in predicting neonatal sepsis

Parameters	Sensitivity %	Specificity %	PPV %	NPV %
CRP	50.0	69.4	38.8	78.1
PCT	92.8	72.2	59.0	96.0

This table shows the sensitivity, specificity, PPV and NPV of CRP and PCT in predicting neonatal sepsis.

Table (7): Distribution of both PCT and CRP level in both preterm and full-term babies with proven and unproven sepsis

Maturity	Unproven sepsis n=108 (%)	Proven sepsis n=42 (%)	P-value
Preterm (84/150)	58/108 (53.7)	26/42 (62.0)	
PCT +ve	19/58 (32.8)	23/26 (88.5)	<0.001*
CRP +ve	14/58 (24.1)	10/26 (38.5)	0.200
Fullterm (66/150)	50/108 (46.3)	16/42 (38.1)	
PCT +ve	10/50 (20.0)	16/16 (100.0)	<0.001*
CRP +ve	16/50 (32.0)	12/16 (75.0)	0.004*

Values present as number and % were analyzed by Fisher exact test. *: Significant.

This table shows significant differences in positive cases of PCT between proven and unproven sepsis regardless the gestational age (P<0.001) whereas, there wase significant difference in positive cases of CRP between proven and unproven sepsis in fullterm group (P=0.004).

Table (8): Comparison of preterm and fullterm babies regarding PCT and CRP levels in both proven and unproven sepsis

Type of sepsis	Preterm n=84 (%)	Fullterm n=66 (%)	P-value
Unproven sepsis (108/150)	58/108 (53.7)	50/108 (46.3)	
PCT +ve	19/58 (32.8)	10/50 (20.0)	0.191
CRP +ve	14/58 (24.1)	16/50 (32.0)	0.395
Proven sepsis (42/150)	26/42 (61.9)	16/42 (38.1)	
PCT +ve	23/26 (88.5)	16/16 (100.0)	0.275
CRP +ve	10/26 (38.5)	12/16 (75.0)	0.029*

Values present as number and % were analyzed by Fisher exact test. *: Significant.

This table shows significant difference between preterm and fullterm babies regarding positive CRP in proven sepsis cases (P=0.029) while insignificant difference regarding PCT.

DISCUSSION

Despite the advances in neonatal care, the neonatal sepsis remains a serious and potentially life-threatening disease. The signs and symptoms of neonatal sepsis may be subtle and nonspecific being clinically indistinguishable from various noninfectious conditions and metabolic disorders. It is the current practice to start empirical antibiotic therapy in all neonates showing infection-like symptoms. However, this may expose newborns to risk of adverse drug effects on one hand and lead to nosocomial complications and the emergence of resistant strains on the other **(Cotton, 2016)**.

Accurate and quick diagnosis is therefore essential so that timely treatment of a potentially fatal disease can be provided and at the same time damages deriving from the unnecessary use of antibiotics can be prevented. Blood culture remains the gold standard for diagnosis of NS, so it is important to develop effective screening tools which can presumably diagnose or exclude neonatal sepsis at the time of presentation and that is why this study was carried out. Recently, the measurement of PCT has been intensively investigated for its diagnostic role in NS with reported high concentration of plasma PCT in infants with severe infection, while PCT levels were very low in those with no infections **(Charles et al., 2018)**.

Our results showed high PCT sensitivity, specificity, PPV and NPV in detecting NS compared to CRP (92.8% Vs 50.0%, 72.2% Vs 69.4%, 59.0% Vs 38.8% and 96.0% Vs 78.1% respectively). These findings coincide with the literature as many authors found that PCT is a promising marker for the diagnosis of NS and PCT sensitivity in the early diagnosis of NS was found to be 83-100% while the specificity was 70-100%. **(Charles et al., 2018**; **Ng and Lam, 2010**; **Schulte et al., 2013)** studied the reliability of PCT concentration in 28 infants who had a severe early onset NS. They found that the sensitivity, specificity, PPV and NPV were 92.6, 95.5, 94.3 and 96.8%, respectively. They also found that 24 infants (> 90%) had PCT levels which were higher than normal at the time of diagnosis. **Vazzalwar et al. (2005)** reported better PCT sensitivity than CRP (97% Vs 72%) and better CRP specificity than PCT (93% Vs 80%) **(Ruan et al., 2018)**.

On the other hand, some researchers questioned the diagnostic accuracy of PCT in

detecting NS. It was reported that serum levels of PCT had also increased in non-infected neonates with perinatal asphyxia, intracranial hemorrhage, pneumothorax, or after resuscitation and these conditions had negatively affected the specificity of PCT **(Janota et al., 2001**, **Kocabas et al., 2007)**.

We tried, in our study, to avoid the influence of noninfectious conditions through strict exclusion criteria. In fact, increase in the serum concentration of CRP is rather slow during the first 24-48 hours of infection and this may negatively affect the sensitivity of the test. In addition, increase in CRP concentration in non-infected clinical conditions such as meconium aspiration and PROM are thought to affect the specificity of the test **(Sakha et al., 2008)**.

In contrary to our results, **Sakha et al.** reported a better role for CRP than PCT in the diagnosis of NS as the sensitivity, specificity, PPV and NPV of CRP (>3.5 mg/L) were 70.4%, 72.2%, 43.2%, and 89% compared to PCT (>2 ng ml) that were 66.7%, 50%, 28.6%, and 83.3% respectively **(Blommendahl et al., 2002)**.

In the same context, **Blommendahl et al. (2002)** reported that although the PCT test appeared to be useful for the diagnosis of NS, it didn't offer any significant advantages over traditional test like CRP for the diagnosis of sepsis, and this was consistent with **Naher et al. (2011)** in that PCT test can be done as an additional test with CRP for the diagnosis of NS.

However, the small sample size of those studies may limit drawing any firm conclusions. Thus, the apparent discrepancy between the various studies could be explained by the geographical differences in infection patterns within the population, the possible interference of other confounders or variations in the study design and bias. Our results revealed that the level of PCT was correlated to the severity of infection as PCT was strong +ve (>10 ng/mL) in most cases of proven sepsis (30/42, 71.4%) and was strong to weak +ve in 28/48 (58.3%) of cases of suspected sepsis while in clinical sepsis most cases has –ve PCT (58/60, 96.7%). These findings come in accordance with **Koksal et al. (2007)** who concluded that the serum PCT level was superior to the serum CRP level in terms of an early diagnosis of NS, in detecting the severity of the illness and in the evaluation of the response to antibiotic treatment **(Kafezis et al., 2005)**.

Despite the PCT test is relatively expensive, it can offer another benefit as the current PCT assay tests are simple, rapid, reliable, specific and of sufficient sensitivity and mostly rise within 4-6 hours of initiation of infection and may help in decisions regarding the need for starting and duration of antibiotic therapy. **(Sucilathangam et al., 2012)** Regarding alteration of other hematological parameters (abnormal TLC, high ESR and abnormal I/T ratio) they were observed only in 14.3%, 7.1% and 14.3% of proven sepsis cases. Similar findings were reported by **Sucilathangam et al. (2012)** in their study of early diagnostic markers for NS as they found the altered hematological parameters were only noticed in 7-14 % of cases **(Hisamuddien et al., 2015)** and so we cannot depend on them for early detection of NS although there are many cases of altered hematological parameters among the total group. PCT is highly specific for bacterial infection, and it helps differentiating it from viral infection. It correlated well with the progression and the severity of the infection. PCT helps in an early diagnosis of the sepsis on the day of the admission itself, before the blood culture report is ready (usually after 3-5 days). PCT helps in avoiding antibiotic therapy where it is not required and thereby reducing the cost and the occurrence of bacterial resistance. PCT can also be employed for the prognosis of sepsis **(Hisamuddien et al., 2015)**.

Our results showed significant elevation of PCT levels compared to elevation in CRP levels among preterm babies with proven sepsis. Hisamuddin et al. discussed validity of CRP for diagnosis of NS and concluded that CRP estimation does have a role in diagnosis of NS but it is not specific enough to be relied upon as the only indicator **(Hisamuddien et al., 2015)**.

CONCLUSION

Our study confirms that PCT is more reliable than CRP in early diagnosis of NS with high sensitivity, specificity, +ve and –ve predictive values. It correlates with the severity of sepsis and allows rapid evaluation of NS rather than waiting for the report of blood culture. Early use of PCT 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 setting will improve efficiency in clinical care and decrease the rising trend of antimicrobial resistance.

LIMITATION OF THE STUDY

This study was subjected to some limitations as absence of control group and the small sample size that might affect the generalization of our data. In addition, the cost of the test precludes its routine use in clinical management of sepsis on the long term, also the unspecific signs of sepsis as tachypnea, bradycardia, tachycardia and feeding intolerance, and the low sensitivity of blood culture which used as the gold standard for diagnosis of sepsis.

RECOMMENDATION

PCT test should be considered for early detection of neonatal sepsis in suspected cases. Further studies are recommended on a larger number of patients

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REFERENCES

1. **Adib M, Bakhshiani Z, Navaei F, Fosoul FS, Fouladi S, Kazemzadeh H. (2012):** Procalcitonin: A Reliable Marker for the Diagnosis of Neonatal Sepsis. Iran J Basic Med Sci; 15: 777–82.
2. **Almudeer AH, Alibrahim MA, Gosadi IM. (2020):** Epidemiology and risk factors associated with early onset neonatal sepsis in the south of KSA. J Taibah Univ Med Sci; 15(6):509–14. doi: 10.1016/j.jtumed.2020.08.009
3. **Alrafiaah A, AlShaalan M, Alshammari F, Almohaisani A, Bawazir A, Omair A. (2016):** Neonatal Sepsis in a Tertiary Care Hospital in Saudi Arabia. Int J Adv Res; 4: 1713–20.
4. **Andi LS, Sánchez PJ, Barbara J. (2017):** Stoll Neonatal sepsis. The Lancet; 390(10104):1770–80.
5. **Blommendahl J, Janas M, Laine S, Mietinen A, Ashorn P. (2002):** Comparison of Procalcitonin with CRP and differential count for diagnosis of culture-proven neonatal sepsis. Scand J Infect Dis; 34: 620–2.
6. **Charles MV, Kalaivani R, Venkatesh S, Kali A, Seetha KS. (2018):** Evaluation of procalcitonin as a diagnostic marker in neonatal sepsis. Indian Journal of Pathology and Microbiology; 61(1):81.
7. **GBD 2015 Child Mortality**

Collaborators (2016): Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet; 388(10053):1725–74. doi: 10.1016/S0140-6736(16)31575-6.

8. **Cotten CM. (2016):** Adverse consequences of neonatal antibiotic exposure. Curr Opin Pediatr; 28(2): 141–9.
9. **Edgar JD, Gabriel V, Gallimore JR, McMillan SA. (2010):** A prospective study of the sensitivity, specificity and diagnosis performance of soluble intercellular adhesion molecule, highly sensitive C-reactive protein, soluble E-selectin and serum amyloid A in the diagnosis of neonatal infection. BMC Pediatr; 10:22. doi: 10.1186/1471-2431-10-22.
10. **EL-Mashad SM, Hamam SM, EL-Farargy MS, and EL-Sharkawy HM. (2019):** Incidence of Neonatal Sepsis and the Causative Organisms in Neonatal Intensive Care Unit of Tanta University Hospital. Med. J. Cairo Univ.; 87(8):5323–32.
11. **Hisamuddin E, Hisam A, Wahid S, Raza G (2015):** Validity of C-reactive protein (CRP) for diagnosis of neonatal sepsis. Pak J Med Sci; 31: 527–31.
12. **Jafar H, Agarwal J, Kumar R, et al. (2019):** Role of serum procalcitonin as a marker for diagnosing neonatal sepsis. IJCP; 6(5): 1991–7.
13. **Janota J, Stranák Z, Bělohlávková S, Mudra K, Simák J. (2001):** Postnatal increase of procalcitonin in premature newborns is enhanced by chorioamnionitis and neonatal sepsis. Eur J Clin Invest; 31: 978–83.
14. **Kafezis DA, Tigani GS, Costalos C. (2005):** Immunologic markers in the neonatal period: diagnostic value and accuracy in infection. Expert Rev Mol Diagn; 5: 231–9.
15. **Kaur K, Mahajan R, Tanwar A. (2013):** A novel marker procalcitonin may help stem the antibiotic overuse in emergency setting. Int J Appl Basic Med Rec; 3: 77–83.
16. **Kocabas E, Sarikcioglu A, Aksaray N, Seydaoglu G, Seyhun Y, Yaman A. (2007):** Role of Procalcitonin, C-reactive protein interleukin -6, interleukin -8 and tumor necrosis factor-∝ in the

diagnosis of neonatal sepsis. Turk J Pediatr; 49: 7–20.

17. **Köksal N, Harmanci R, Cetinkaya M, Hacimustafaoğlu M. (2007):** The roles of procalcitonin and CRP in the diagnosis and the follow up of neonatal sepsis cases. Turk J Pediatr; 49: 21–9.

18. **Machado JR, Soave DF, da Silva MV, et al. (2014):** Neonatal sepsis and inflammatory mediators. Mediators Inflamm; 2014:269681. doi:10.1155/2014/269681

19. **Mishra UK, Jacobs SE, Doyle LW, Garland SM. (2006):** Newer approaches to the diagnosis of early onset neonatal sepsis. Arch Dis child Fetal Neonatal Ed; 91: F208.

20. **Naher BS, Mannan MA, Noor K, Shahiddullah M. (2011):** Role of serum Procalcitonin and CReactive Protein in the diagnosis of neonatal sepsis. Bangl Med Res Counc Bull; 3792: 40–6.

21. **Ng PC. and Lam HS. (2010):** Biomarkers for late-onset neonatal sepsis: cytokines and beyond. Clinics in Perinatology; 37(3): 599–610.

22. **Pontrelli, G., De Crescenzo, F., Buzzetti, R. et al. (2017):** Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC Infect Dis; 17: 302.

23. **Rodwell RL, Leslie AL, Tudehope DI. (1988):** Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr; 112:761–7. doi: 10.1016/S0022-3476(88)80699-1

24. **Ruan L, Chen GY, Liu Z, et al. (2018):** The combination of procalcitonin and C-reactive protein or presepsin alone improves the accuracy of diagnosis of neonatal sepsis: a meta-analysis and systematic review. Crit Care; 22(1):316.

25. **Sakha K, Husseini MB, Seyyedsadri N. (2008):** The role of procalcitonin in the diagnosis of Neonatal sepsis and the correlation between procalcitonin and C-reactive protein in these patients. Pak J Biol Sci; 11: 1785–90.

26. **Schulte W. Bernhagen J. and Bucala R. (2013):** Cytokines in sepsis: potent immunoregulators and potential therapeutic targets—an updated view," Mediators of Inflammation; 165974: 1–16.

27. **Seliem WA and Sultan AM. (2018):** Etiology of early onset neonatal sepsis in neonatal intensive care unit - Mansoura, Egypt. J Neonatal Perinatal Med; 11(3):323–30. doi: 10.3233/NPM-17128

28. **Shriazi H, Riaz S, Taher R. (2010):** Role of the Hematological Profile in Early Diagnosis of Neonatal Sepsis. Ann Pak Inst Med Science; 6: 152–6.

29. **Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. (2011):** Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics; 127(5):817–26.

30. **Sucilathangam G, Amuthavalli K, Velvizhi G, Ashihabegum MA, Jeyamurugan T, Palaniappan N. (2012):** Early Diagnostic Markers for Neonatal Sepsis: Comparing Procalcitonin (PCT) and C-Reactive Protein (CRP). J Clin Diagn Res; 6: 627–31.

31. **Vazzalwar R, Pina-Rodrigues E, Puppala BL, Angst DB, Schweig L. (2005):** Procalcitonin as a screening test for late-onset sepsis in preterm, very low birth weight infants. J Perinatol; 25: 397–402.

32. **Whicher J, Beinvenu J, Monneret G. (2001):** Procalcitonin as an acute phase marker. Ann Clin Biochem; 38: 483–93.