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Assessment of C-Reactive Protein in the Early Diagnosis of Neonatal Sepsis in a Rural Area in Tikrit

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ABSTRACT

Background: In most of the cases of neonatal sepsis the diagnosis is delayed until late stages of the diseases & end often in complications & death. The late diagnosis is due to the fact that the early signs are neither specific nor sensitive. The problem of delayed diagnosis and treatment is more prevalent & much longer in rural areas which are away from health care facilities. Recently, reliable & early diagnosis of neonatal sepsis has become a challenging topic in the medical discussion. The gold standard test for neonatal sepsis is the blood culture. However, blood culture is restricted by the drawback of false negative results & time-consuming investigation. C-reactive protein (CRP), a pentraxin protein, plays an essential job in inflammatory and/or infectious stimuli, thus being considered as an acute-phase protein in neonatal sepsis. Because the early diagnostic value of CRP is still a matter of debate when used for the diagnosis of neonatal sepsis. The aim of this study is to evaluate the diagnostic value of CRP in early diagnosis of neonatal sepsis in rural area.

Patients & Methods: A cross sectional outpatient based research was carried out on 100 neonates suspected to have early sepsis examined in the private clinic in some rural areas in Al-Alam district. These rural areas in Iraq are away from health care services & the people suffer from poverty, so that the families can't admit their sick children to hospital. Usually they want to treat their children at home on their own responsibility. This study is a necessity method for treating special conditions in exceptional circumstances that prevent them from following the approved medical rules, such as in-hospital treatment and using cheap, simple and rapid investigation. The period of the study was one year from 1st May 2020 to 1st May 2021. The patient's inclusion criteria were neonates of age less than 28 days of life with manifestations of sepsis. The patient's exclusion criteria were neonates with previous treatment with antibiotics, congenital anomalies or any other diseases other than sepsis. A questionnaire was developed and contained the clinical information about the patients. Detailed history was taken from each family which includes age, sex, maturity, residence, weight, risk factors and clinical presentations of neonatal sepsis. Investigations C-reactive protein was done for all neonates. These neonates received antibiotic therapy of combination (Gentamicin 5mg/kg plus ampicillin 200 mg/kg) or (3rd generation cephalosporin 100mg/kg plus Ampicillin 200 mg/kg) based on the clinical examination and CRP result. Follow up carried out by clinical examination and serial CRP which done after 1 week.

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Introduction:

One of the common severe bacterial infection of the bloodstream of neonates is Neonatal sepsis, and responsible for high morbidity and high mortality.[1] Annually neonatal sepsis is causes greater than 520,000 neonatal deaths. [2] The early diagnosis is the main indicator of the outcome of neonatal sepsis management. In most of the cases of neonatal sepsis the diagnosis is delayed until late stages of the diseases & end often in complications & death.[3] The late diagnosis is due to the fact that the early signs are neither specific nor sensitive. The problem of delayed diagnosis and treatment is more prevalent & much longer in rural areas which are away from health care facilities. Neonatal sepsis is divided into two classes: early-onset sepsis (72hr) and late onset neonatal sepsis after 72 hours. Recently, reliable & early diagnosis of neonatal sepsis has become a challenging topic in the medical discussion.[4] The gold standard test for neonatal sepsis is the blood culture. However, blood culture is restricted by the drawback of false negative results and time-consuming investigation. [1, 5]

Now, several biochemical markers, like C-reactive protein (CRP), procalcitonin (PCT), and tumor necrosis factor alpha (TNF-α), have been suggested as potential markers for neonatal sepsis diagnosis. [6] C-reactive protein (CRP), a pentraxin protein, plays an essential job in inflammatory and/or infectious stimuli, thus being considered as an acute-phase protein in neonatal sepsis. Previously researches have revealed that CRP is a beneficial diagnostic indicator for the early stages of neonatal sepsis. Another research has showed that CRP is the best unique indicator of neonatal sepsis in the first 48 hours of onset, with high specificity & sensitivity. However, Benitz et al. thought that the positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infections. [7] What's more, CRP has also been found just in the laboratory test the best method for the diagnosis of neonatal sepsis. So, the early diagnostic value of CRP is still a

matter of debate when used for the diagnosis of neonatal sepsis.[1, 8, 9] The aim of this study is to evaluate the diagnostic value of CRP in early diagnosis of neonatal sepsis in rural area.

Patients and Methods:

A cross sectional outpatient based research was carried out on 100 neonates suspected to have early sepsis examined in the private clinic in some rural areas in Al-Alam district. These rural areas in Iraq are away from health care services & the people suffer from poverty, so that the families can't admit their sick children to hospital. Usually they want to treat their children at home on their own responsibility. This study is a necessity method for treating special conditions in exceptional circumstances that prevent them from following the approved medical rules, such as in-hospital treatment and using cheap, simple and rapid investigation. Inclusion criteria include full term neonates with suspicion of neonatal sepsis without any other disease.

This research is based on Gyllensvärd, J in 2020 study revealed that C-reactive protein- and clinical symptoms-guided decision-making for early onset neonatal sepsis significantly decreased the duration of antibiotic therapy and hospital stay, and hence reduced healthcare costs, with no reinfection in a cohort of term infants.[1, 10]

The period of the study was one year from 1st May 2020 to 1st May 2021. The patient's inclusion criteria were neonates of age less than 28 days of life with manifestations of sepsis. The patient's exclusion criteria were neonates with previous treatment with antibiotics, congenital anomalies or any other diseases other than sepsis. A questionnaire was developed and contained the clinical information about the patients. Detailed history was taken from each family which includes age, sex, maturity, residence, weight, risk factors and clinical presentations of neonatal sepsis. Investigations C-reactive protein was done for all neonates. According to Seale AC et al in 2015 that stated the new treatment guidelines the intravenous antibiotic therapy can be withdrawn after three

days followed by administration of oral suspension antibiotic (Amoxicillin, 20 mg/kg three times a day) for two more days in term neonates meeting the criteria of the new treatment guidelines. The new guidelines contained the following criteria; Term neonate, and no need of intensive care (including invasive respiratory support or cardiovascular support) initially when the antibiotic treatment started, and the neonate appeared well on day 3, and the blood culture was not positive on day 3, & Maximum CRP-value of 80 mg/L decreasing by at least 50% during the first three days. [11] For extra safety, the infants included in the study also received a routine visit on day 7 for clinical assessment and control of CRP. These neonates received antibiotic therapy of combination (Gentamicin 5mg/kg plus ampicillin 200 mg/kg) or (3rd generation cephalosporin 100mg/kg plus Ampicillin 200 mg/kg) based on the clinical examination and CRP result. Follow up carried out by clinical examination and serial CRP which done after 1 week. A positive CRP is a level equal or more than 6 mg/L. [12, 13]

Results:

This research includes 100 full term, neonates attended private clinic with minimal signs and symptoms neonatal sepsis. Every neonate was assessed by history, clinical assessment and C-reactive protein (CRP) was done for all cases. Table 1 reveals the demographic features of study sample, it was clear from the table that (60%) of the study population was in the first week of life, on the other hand only 5% of patients who have sepsis were in their fourth week of life. Male gender constituted 65% of patients with sepsis compared to 35% of female group. Weight of equal to 2.5 Kg or more constituted 70% of the study population. Most of neonatal sepsis cases occur in occur in normal birth weight patients 70% versus 30% in low birth weight.

Most of the study population was products of 70% Cesarean Section while normal vaginal delivery 30 (30 %).

Table 1: Demographic Features of the Study Sample

Gender		
Female	35	35%
Male	65	65%
Residence		
Rural	100	100%
Urban	0	0%
Delivery mode		
Normal vaginal	30	30%
CS	70	70%
Maternal Risk Factors of Neonatal Sepsis		
Positive		70%
Negative		30 %
Age group		
1-7 days	60	60%
8-14	20	20%
15-21	15	15%
22-28	5	5%
Body weight		
≥ 2.5	70	70%
< 2.5	30	30%

Table 2 shows the main presenting symptoms among the study population as followings; fever present in 85% of the cases, poor feeding 80%, vomiting 66%, poor activity 66% & poor cry 40%.

Table 2: Presenting signs and symptoms in the study sample.

Presentations	**Neonatal Sepsis No. %**	
Fever	85	85%
Poor feeding	80	80%
Poor reflex	70	70%
Vomiting	66	66%
Lethargy	46	46%
Poor cry	40	40
Umbilical discharge	10	10%

Table 3 reveals that bad antenatal care was reported in 85% of the cases, maternal fever was present in 77%, and PROM reported in 30%.

Table 3: Maternal Risk Factors of Neonatal Sepsis.

Risk factor	No	%
Bad Antenatal Care	85	85%
Maternal fever	77	77%
PROM	30	30%
Meconium stained liquor	13	13%
Umbilical discharge	10	10%

The CRP level return to negative in 70% of cases CRP after 72 hours of antibiotic therapy, while high level of CRP in about 30% of patients persists until the 7 days of antibiotic therapy & this indicate the beneficial of CRP in treatment follow up.

Table 4: Serial CRP Measurements on day 0, 3, 7

CRP	Initial CRP		Day 3 CRP		Day 7 CRP	%
	F	%	F	%	F	%
CRP ≥6mg/L	100	100	30	30	0	0
CRP < 6mg/L	0	0	70	70	100	100

X^2=212.9, df =2, P value < 0.05

Discussion

Depending only on the clinical features for the neonatal sepsis diagnosis is dangerous and hard to establish, although it is essential to start antibiotic therapy as early as possible due to its high mortality. Presence of high index of suspicion in dealing with such cases in presence of minimal clinical features especially in presence of maternal risk factors is necessary in preventing high mortality from neonatal sepsis. This is highly important in special circumstances like rural areas of restricted access to health services. There male predominance in the current study is similar to studies by Khassawneh M & Manucha V. [14, 15]

This result may be explained by impaired defense mechanisms and low immunoglobulin G levels in boys. [16] All the study sample of patients (100) at examination had high serum CRP level and the treatment started. The current

study revealed that CRP is an effective method for diagnosis of neonatal sepsis and follow up of antibiotic therapy. This is similar to Hofer N in 2012, & Klingenberg C in 2018 who found that CRP as it is fast, cost-effective and simple in diagnosis and utilizing CRP is a useful guide to help clinicians to discontinue antibiotic therapy.[17, 18]

The current study revealed that CRP level return to negative in 70% of cases CRP after 72 hours of antibiotic therapy, while high level of CRP in about 30% of patients persists until the 3 days of antibiotic therapy & this indicate the beneficial of CRP in treatment follow up. In a cohort of 60 neonates with early-onset sepsis, Ehl et al found that after effective antibiotic treatment, [19] CRP values further increased, peaking and consecutively decreasing after 16 hrs. A CRP level that returned to the normal range may indicate that antibiotic was effective, allowing its discontinuation, provided that the clinical condition of the neonate has improved and culture results were negative. [20] The current study proved serial CRP measurements is beneficial in follow up. This supported by another benefit CRP is the follow up of the neonatal sepsis by serial CRP measurements. The serial measurements of CRP will be of advantage in in monitoring the response to antibiotic therapy and to define the antibiotic therapy duration. [21, 22]

The current study stated that PROM was reported in 30% of cases and this is similar to Parker, Margaret M et al in 2019 and M. T. Utomo in 2016 showed that premature rupture of membrane was significantly associated with the risk of neonatal sepsis. [23, 24] The current study stated that 77% of cases had maternal fever and this is similar to Oliveira et al in 2016 found that infection of the genitourinary tract and premature rupture of fetal membranes were the main gestational risk factors involved in neonatal sepsis. Therefore, the identification of the risk factors associated to the diagnosis of neonatal sepsis may contribute to interventions and research that helps to reduce neonatal mortality resulting from these risks. [25] The current study stated that

85% of cases had bad antenatal care and this is similar to Parker, Margaret M et al in 2019 who found that the majority, 86 (83.5%), of mothers who utilized ANC services had neonates among cases, though antenatal care utilization is vital in lessening the risk factors of adverse birth outcomes including newborn sepsis. But it is different from the study findings by Siakwa et al. [26] in Ghana and Gebremedhin, Berhe, and Gebrekirstos in Ethiopia did not observe antenatal service utilization as a risk factor of neonatal sepsis. The present study findings are congruent with the above study findings in Ghana and Ethiopia. [27]

Conclusion: The current research concluded that CRP is reliable, rapid, & cheap test in the early diagnosis of neonatal sepsis that allows early treatment and obtaining better disease outcome.

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