

EVALUATION OF POSITIVITY OF CRP TEST IN EARLY ONSET NEONATAL SEPSIS IN RELATION TO DURATION OF PROM VS PROM DELIVERY INTERVAL (PDI)

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Abstract

Early onset infections are caused by organism prevalent in the maternal genital tract or in the delivery area. PROM is rupture of membranes before the onset of labour after 37 completed weeks of gestation. Intra amniotic infection is an acute inflammation of the membrane and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture. Hence based on above conditions the present study was planned for Evaluation of Positivity of CRP test in early Onset Neonatal Sepsis in Relation to Duration of PROM vs PROM Delivery Interval (PDI).

The present study was planned in Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India. The study was planned from November 2018 to June 2019. In the present study 50 mothers attended t antenatal clinic towards term pregnancy with history of leaking or confirmed PROM were enrolled. Clinical PROM was confirmed by speculum examination and the duration was recorded. All cases managed actively and the interval between PROM and delivery were recorded in obstetric unit of this hospital.

The data generated from the present study concludes that even if 6 hour PROM is high risk for EONS, PDI should be considered first before PROM. So that, we will be more cautious and supportive and use of antibiotics in treatment to prevent need for neonatal intensive care without increase in perinatal morbidity and mortality.

Keywords: Early onset Sepsis (EOS), C- Reactive Protein (CRP), Premature rupture of membrane(PROM) PROM delivery interval(PDI), etc.

Introduction

Neonatal sepsis may be categorized as early onset (day of life 0-3) or late onset (day of life 4 or later). Of newborns with early-onset sepsis, 85% present within 24 hours (median age of onset 6 hours), 5% present at 24-48 hours, and a smaller percentage present within 48-72 hours. Onset is most rapid in premature neonates.

Early-onset sepsis is associated with acquisition of microorganisms from the mother. Infection can occur via hematogenous, transplacental spread from an infected mother or, more commonly, via ascending infection from the cervix. Organisms that colonize the mother's genitourinary (GU) tract may be acquired by the neonate as it passes through the colonized birth canal at delivery. The microorganisms most commonly associated with early-onset infection include the following [1] : Group B Streptococcus (GBS); Escherichia coli; Coagulase-negative Staphylococcus; Haemophilus influenza; Listeria monocytogenes.

Trends in the epidemiology of early-onset sepsis show a decreasing incidence of GBS disease following the widespread adoption of prenatal screening and treatment protocols. [2, 3, 4]

In a study involving 4696 women, prenatal cultures showed a GBS colonization rate of 24.5%, with a positive culture rate of 18.8% at the time of labor. [5] As many as 10% of prenatally culture-negative women were found to have positive cultures at the time of labor. In the study, intrapartum antibiotic prophylaxis occurred appropriately in 93.3% of cases, with 0.36 of 1000 infants developing early-onset GBS disease. [5]

Trends in late-onset sepsis show an increase in coagulase-negative streptococcal sepsis, with most isolates showing susceptibility to first-generation cephalosporins. [2] The infant's skin, respiratory tract, conjunctivae, gastrointestinal tract, and umbilicus may become colonized via contact with the environment or caregivers.

Pneumonia is more common in early-onset sepsis, whereas meningitis and bacteremia are more common in late-onset sepsis. Early-onset sepsis is 10 to 20 times more likely to

occur in premature, very low birthweight infants. [6] Premature infants often have nonspecific, subtle symptoms; considerable vigilance is therefore required in these patients so that sepsis can be identified and treated in a timely manner.

The infectious agents associated with neonatal sepsis have changed since the mid-20th century. During the 1950s, *S aureus* and *E coli* were the most common bacterial pathogens among neonates in the United States. Over the ensuing decades, Group B *Streptococcus* (GBS) replaced *S aureus* as the most common gram-positive organism causing early-onset sepsis.

Currently, GBS and *E coli* continue to be the most commonly identified microorganisms associated with neonatal infection. Additional organisms, such as coagulase-negative *Staphylococcus epidermidis*, *L monocytogenes*, *Chlamydia pneumoniae*, *H influenzae*, *Enterobacter aerogenes*, and species of *Bacteroides* and *Clostridium* have also been identified in neonatal sepsis.

Meningoencephalitis and neonatal sepsis can also be caused by infection with adenovirus, enterovirus, or coxsackievirus. Additionally, sexually transmitted diseases (eg, gonorrhea, syphilis, herpes simplex virus [HSV] infection, cytomegalovirus [CMV] infection, hepatitis, human immunodeficiency virus [HIV] infection, rubella, toxoplasmosis, trichomoniasis, and candidiasis) have all been implicated in neonatal infection.

Bacterial organisms with increased antibiotic resistance have emerged and have further complicated the management of neonatal sepsis. [7] The colonization patterns in nurseries and personnel are reflected in the organisms currently associated with nosocomial infection. In neonatal intensive care units (NICUs), infants with lower birth weight and younger gestational ages have an increased susceptibility to these organisms.

S epidermidis, a coagulase-negative *Staphylococcus*, is increasingly seen as a cause of nosocomial or late-onset sepsis, especially in the premature infant, in whom it is considered the leading cause of late-onset infections. Its prevalence is likely related to several intrinsic properties of the organism that allow it to readily adhere to the plastic mediums found in intravascular catheters commonly required for the care of these infants.

The bacterial capsule polysaccharide adheres well to the plastic polymers of the catheters. Also, proteins found in the organism (AtIE and SSP-1) enhance attachment to the surface of the catheter. The adherence creates a capsule between microbe and catheter, preventing C3 deposition and phagocytosis. [8, 9]

Biofilms are formed on indwelling catheters by the aggregation of organisms that have multiplied under the

protection provided by the adherence to the catheter. Slimes are produced at the site from the extracellular material formed by the organism, which provides a barrier to host defense as well as to antibiotic action, making coagulase-negative staphylococcal bloodstream infection (BSI) more difficult to treat. The toxins formed by *S epidermidis* have also been associated with necrotizing enterocolitis.

In addition to being a cause of neonatal sepsis, coagulase-negative *Staphylococcus* is ubiquitous as part of the normal skin flora. Consequently, it is a frequent contaminant of blood and cerebrospinal fluid (CSF) cultures. When a culture grows this organism, the clinical presentation, colony counts, and the presence of polymorphonuclear neutrophils (PMNs) on Gram staining of the submitted specimen often help differentiate true infection from contaminated culture specimens.

In addition to the specific microbial factors mentioned above, numerous host factors predispose the newborn to sepsis. [10] These factors are especially prominent in the premature infant and involve all levels of host defense, including cellular immunity, humoral immunity, and barrier function. Immature immune defenses and environmental and maternal factors contribute to the risk for neonatal sepsis, morbidity, and mortality, particularly in preterm and/or very low birthweight (VLBW) infants. [10, 11] There may also be a genetic association. [10]

The incidence of culture-proven early-onset sepsis in the United States is approximately 0.3-2 per 1000 live births. Of the 7%-13% of neonates who are evaluated for neonatal sepsis, only 3%-8% of those screened will have culture-proven sepsis. This disparity arises from the cautious approach to management of neonatal sepsis. [12]

Because early signs of sepsis in the newborn are nonspecific, diagnostic studies are often ordered and treatment initiated in neonates before the presence of sepsis has been proven. Moreover, because the American Academy of Pediatrics (AAP), [13] the American College of Obstetricians and Gynecologists (ACOG), [14] and the Centers for Disease Control and Prevention (CDC) [15] all have recommended sepsis screening or treatment for various risk factors related to Group B *Streptococcus* (GBS) infections, many asymptomatic neonates now undergo evaluation and are exposed to antibiotics.

Premature infants have an increased incidence of sepsis, with a significantly higher occurrence in infants with a birth weight lower than 1500 g (11-22.7 per 1000 live births) than in infants born at 37 weeks or later (0.3-0.98 per 1000 live births). The risk of death or meningitis from sepsis is higher in infants with low birth weight than in full-term neonates.

Black infants have an increased incidence of GBS disease and late-onset sepsis. This is observed even after other risk factors such as low birth weight and younger maternal age have been controlled for. This finding may be in part due to higher carriage rates of GBS among black women, but this factor does not explain all of the variation. [16] In all races, the incidence of bacterial sepsis and meningitis, especially with gram-negative enteric bacilli, is higher in males than in females.

With early diagnosis and treatment of neonatal sepsis, most term infants will not experience associated long-term health problems. However, if early signs or risk factors are missed, mortality increases. Residual neurologic damage occurs in 15%-30% of neonates with septic meningitis.

Mortality from neonatal sepsis may be as high as 50% for infants who are not treated. Infection is a major cause of mortality during the first month of life, contributing to 13%-15% of all neonatal deaths. Low birth weight and gram-negative infection are associated with worse outcomes. Neonatal meningitis occurs in 2-4 cases per 10,000 live births and contributes significantly to mortality from neonatal sepsis; it is responsible for 4% of all neonatal deaths.

In preterm infants who have had sepsis, impaired neurodevelopment is a concern. Proinflammatory molecules may negatively affect brain development in this patient population. In a large study of 6093 premature infants who weighed less than 1000 g at birth, preterm infants with sepsis who did not have meningitis had higher rates of cerebral palsy (odds ratio [OR] 1.4-1.7), developmental delay (OR 1.3-1.6), and vision impairment (OR 1.3-2.2) as well as other neurodevelopmental disabilities than infants who did not have sepsis. [17]

Infants with meningitis may acquire hydrocephalus or periventricular leukomalacia. They may also have complications associated with the use of aminoglycosides, such as hearing loss or nephrotoxicity.

Mortality from untreated sepsis can be as high as 50%, leading many clinicians to err on the side of treating asymptomatic infants based on historical and maternal risk factors alone. This approach has been questioned in the past several years as more evidence emerges on the deleterious impact of unnecessary antibiotic exposure, including interference with the establishment of breast feeding, alternations in gut microbiome, increases in the incidence of childhood obesity, and development of antimicrobial resistance, amongst others. [26]

Early onset infections are caused by organism prevalent in the maternal genital tract or in the delivery area. PROM is rupture of membranes before the onset of labour after 37 completed weeks of gestation. Intra amniotic infection is an acute inflammation of the membrane and chorion of

the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture. Hence based on above conditions the present study was planned for Evaluation of Positivity of CRP test in early Onset Neonatal Sepsis in Relation to Duration of PROM vs PROM Delivery Interval (PDI).

Methodology:

The present study was planned in Department of Pediatrics, Nalanda Medical College and Hospital, Patna, Bihar, India. The study was planned from November 2018 to June 2019. In the present study 50 mothers attended t antenatal clinic towards term pregnancy with history of leaking or confirmed PROM were enrolled. Clinical PROM was confirmed by speculum examination and the duration was recorded. All cases managed actively and the interval between PROM and delivery were recorded in obstetric unit of this hospital.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: All pregnant women attended antenatal clinic in third trimester with cofirmed premature rupture of membrane. All babies diagnosed as EONS ((The confirmed (Blood culture + but CRP -ve) and suspected cases(CRP positive ± clinical feature suggestive of EONS) and absent cases (CRP negative but clinical feature suggestive of EONS)).

Exclusion Criteria: Pregnant women with other complication except PROM attended antenatal clinic Neonatal complication other than EONS admitted in NICU

Results & Discussion:

Early onset infections are caused by organism prevalent in the maternal genital tract or in the delivery area. PROM is rupture of membranes before the onset of labour after 37 completed weeks of gestation. Intra amniotic infection is an acute inflammation of the membrane and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture.

CRP binds to the phosphocholine expressed on the surface of dead or dying cells and some bacteria. This activates the complement system, promoting phagocytosis by macrophages, which clears necrotic and apoptotic cells and bacteria. [18]

This so-called acute phase response occurs as a result of increasing concentrations of IL-6, which is produced by macrophages as well as adipocyte in response to a wide range of acute and chronic inflammatory conditions such

as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis. These conditions cause release of interleukin-6 and other cytokines that trigger the synthesis of CRP and fibrinogen by the liver.

CRP binds to phosphocholine on micro-organisms. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages (opsonin-mediated phagocytosis), which express a receptor for CRP. It plays a role in innate immunity as an early defence system against infections. [18]

Spontaneous rupture of membranes at any time beyond 28 weeks of pregnancy but before the onset of labor is called premature rupture of membranes (PROM). Term prelabor rupture of membranes is the condition where the bag of membranes ruptures before the onset of labor. This poses significant risk to the mother and the fetus. Preterm PROM is one of the important causes of preterm birth where prematurity in addition to PROM can predispose to high perinatal morbidity and mortality along with maternal morbidity. Early identification of sepsis is essential. The duration of leaking, 3 or more vaginal examinations after the rupture of membrane, is a significant risk factor for neonatal sepsis. [19-20]

The mother has the risk of chorioamnionitis and puerperal sepsis, and the neonate is at the risk of early-onset sepsis. The morbidity increases as there are more chances of operative delivery. Early diagnosis of chorioamnionitis and neonatal sepsis can reduce maternal and neonatal morbidity. [21]

C-reactive protein (CRP) is a serum protein which is synthesized in liver. Its rate of synthesis and secretion increases many times within few hours of injury or onset of inflammation and may reach up to 20 times. CRP is a blood test marker for inflammation in the body. [20-22]

A wide variety of acute phase reactant has been evaluated in neonate with suspected bacterial sepsis. However, only C-reactive protein (CRP) and procalcitonin concentration have been investigated in sufficiently largely studies. [23] C-reactive protein is a substance produced by the liver that increases in the presence of inflammation in the body. CRP named for its capacity to precipitate the somatic C-polysaccharide of streptococcus pneumonia, was the first acute phase protein to be described and is an exquisitely sensitive marker of early infection and tissue damage. This response appears much earlier than the pyrogen response leading to constitutional symptoms and signs. Whereas, a single blood culture in a sufficient value is required for all neonates with suspected sepsis to confirm sepsis.

Table 1: Basic Details

Parameters	No. of Cases
Gestation Age:	
Pre Term	29
Term	21
Sex:	
Males	26
Females	24
Early Onset Neonatal Sepsis:	
Confirmed	38
Absent	12

Table 2: PROM and CRP Cases

Duration of PROM (hr)	Total	CRP Positive
0 – 6	35	12
6 – 12	9	4
12 – 24	5	5
24 – 48	1	1
Total	50	22

Table 3: PROM delivery Interval (PDI) and CRP

PROM delivery Interval(PDI) (hr)	Total	CRP Positive
0 – 12	12	6
12 – 24	29	9
24 – 48	8	6
24 – 48	1	1
Total	50	22

Khade and Bava [24] in their study reported maternal morbidity as 16% and perinatal morbidity as 33%. The most common causes were hyperbilirubinemia (23%) and respiratory distress syndrome (RDS) (21%). Perinatal mortality occurred in 15%. It was mainly due to RDS (53%). 25% neonates were delivered by cesarean. The most common indication for cesarean was malpresentation (36%) followed by fetal distress (24%).

Sharma and Dey reported in 2017 that the incidence of rupture of membrane in their study was 4.2%. [25] They reported that 92% of patients delivered within 24 h of rupture of membrane and 18% of them required cesarean section. Five neonates had RDS and one neonate had sepsis. They reported the induction of labor and delivery within 24 h of rupture of membranes associated with low incidence of maternal and neonatal adverse outcome.

Maternal and peripartum risk factors influence early onset neonatal sepsis. The most frequent risk factors are chorioamnionitis and maternal systemic infection. [26-27] Intrauterine infection increases morbidity and mortality of diseases such as severe maternal infectious shock, disseminated intravascular coagulopathy, adult respiratory distress syndrome (RDS), and renal failure. [28] Also, intrauterine infection and inflammation induce preterm labor at least one-third of spontaneous preterm deliveries. [29-30]

Simple, rapid, noninvasive, and safe tests of markers of intrauterine infection could be useful in prediction of

morbidity among pregnant women, with or without labor. If maternal infections during pregnancy are diagnosed and treated early, the mortality and morbidity of neonates should be decreased.

Conclusion:

The data generated from the present study concludes that even if 6 hour PROM is high risk for EONS, PDI should be considered first before PROM. So that, we will be more cautious and supportive and use of antibiotics in treatment to prevent need for neonatal intensive care without increase in perinatal morbidity and mortality.

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