Procalcitonin versus CRP as an early indicator of fetal infection in preterm premature rupture of membranes

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The aim of this study was to examine the diagnostic sensitivity and specificity of C-reactive protein (CRP) and procalcitonin (PCT) in neonates who were born after preterm premature rupture of membranes (PPROM) and compare these with interleukin-6 (IL-6). The study involved 74 preterm neonates who were born after PPROM. IL-6, CRP, complete blood count and leukocyte ratios, and PCT levels were measured in the 1st day of life, and CRP, PCT, and blood counts were repeated on the 3rd day of life. Seventy-four infants with PPROM were divided into two groups according to the development of sepsis and infection (Group 1: sepsis, n=32; Group 2: no sepsis, n=42). There were no significant differences between these groups with respect to gestational age, birthweight and duration of membrane rupture. There were significant differences between the two groups in the 1st day CRP (Group 1: 0.85 ± 1.36 mg/dl, Group 2: 0.23 ± 0.25 mg/dl; p=0.016), 1st day PCT (Group 1: 7.2 ± 7.6 ng/ml, Group 2, 1.6 ± 4.0 ng/ml; p<0.001), and 3rd day PCT (Group 1: 9.01 ± 11.5 ng/ml, Group 2: 1.34 ± 1.35 ng/ml; p=0.001) and IL-6 (Group 1: 80.7 ± 67.2 pg/ml, Group 2: 3.4 ± 3.5 ng/ml; p<0.001) levels. CRP levels were not significantly different between Group 1 (1.2 ± 1.7 mg/dl) and Group 2 (0.58 ± 1.1 mg/dl) on the 3rd day of life (p=0.059). CRP levels on the 1st day of life had a cut-off value of 0.72 mg/dl with a sensitivity and specificity of 56% and 58%, respectively. CRP levels on the 3rd day had a cut-off level of 0.78 mg/dl with 60% sensitivity and 63% specificity. PCT levels had a cut-off level of 1.74 ng/ml with 76% sensitivity and 85% specificity on the 1st day of life, and of 1.8 with 89% sensitivity and 86% specificity on the 3rd day of life. Statistical analysis revealed that the cut-off value of 7.6 pg/ml for IL-6 had a 93% sensitivity and 96.7% specificity.

Interleukin (IL)-6 is the most reliable marker for the detection of early-onset sepsis in preterm neonates with PPROM. Early PCT levels seemed to be more sensitive than early CRP in this population.

Key words: preterm premature rupture of membranes, C-reactive protein, procalcitonin, interleukin-6, sepsis, infection.

Premature rupture of membranes (PROM) refers to membrane rupture before the onset of uterine contractions, and preterm PROM (PPROM) is the term used when PROM is presented and the gestation is less than 37 completed weeks. PPROM occurs in 3% of pregnancies and is responsible for approximately one-third of preterm births[1].

Preterm premature rupture of membranes is a predisposing factor for serious maternal infections such as intra-amniotic infection, endometritis or septicemia. The fetus is at a greater risk of PPROM-related morbidity and mortality than the mother. Fetal infections may appear as early neonatal infections such as pneumonia, meningitis and sepsis and are associated with a serious increase in mortality and morbidity in preterm neonates[2]. Neurodevelopmental delay and cerebral palsy are potential long-term sequelae. Preterm neonates who develop early infection commonly have subtle and non-specific clinical symptoms.

Increasing use of antenatal and intrapartum antibiotics for the prevention of neonatal infection may result in false-negative cultures of blood and cerebrospinal fluid, making the diagnosis of sepsis difficult[1]. Neonatal infection needs to be diagnosed by laboratory tests other than cultures and by the diagnostic acumen of the physician.

Given the severity of neonatal infections and their imminent fatality, these limitations lead to aggressive use of antibiotics and prolonged hospital stay. Novel infection markers might be of substantial value in the management of such cases. Interleukin-6 (IL-6) is a cytokine that is produced during inflammation and plays an important role in host defense to invasive infection[3-5]. It is also produced by a variety of cells, including endometrial stromal, amnion, chorion, and decidual cells, and is transported by a carrier protein that cannot pass through the placenta[3,4]. Previous studies have shown IL-6 to be the best marker of fetal inflammation and an early and reliable marker of neonatal infection[6]. Researches have confirmed that IL-6 concentrations in amniotic fluid are good indicators of microbial invasion of the amniotic cavity and the best marker of fetal inflammation[7]. However, widespread use of the IL-6 concentration as a marker is limited due to its high cost. Other infection markers such as procalcitonin (PCT) and C-reactive protein (CRP) are cheaper, quick methods and are routinely used in neonatal intensive care units to evaluate sepsis and early infections[8]. The purpose of this study was to determine the predictive value of CRP and PCT for fetal inflammation and to compare results with IL-6 in neonates with a history of PPROM.

Material and Methods

Patients

Preterm neonates with a history of PPROM, born between November 2007 and December 2008 in Hacettepe University Hospital, Ankara, Turkey, were included in the study. All the neonates were evaluated for clinical and laboratory findings of sepsis at birth. Blood was taken from the umbilical vein for complete blood count, CRP, PCT, IL-6 levels, and blood culture. Empiric antibiotic treatment was given according to the department policy. On the 3rd day of life, a repeat blood specimen was obtained for the measurement of CRP and PCT levels. Neonates with major congenital abnormalities were excluded from this study. Data collected on pregnancy and labor included maternal illnesses, obstetric complications, duration of PPROM, maternal antibiotic treatment, tocolytic therapy, antenatal corticosteroid use, and clinical chorioamnionitis. Clinical chorioamnionitis was defined when maternal temperature was 38°C or higher and at least two of the following factors were present: uterine tenderness, foul-smelling amniotic fluid, increased white blood cell count, and maternal or fetal tachycardia[9].

Preterm premature rupture of membranes was defined as the rupture of fetal chorioamniotic membranes before (at least 24 hours) the onset of labor in the preterm gestational age group.

Infants with PPROM were divided into two groups according to the development or not of sepsis during the first days of life. Proven sepsis was defined in the presence of a positive blood culture associated with clinical findings such as apnea-tachypnea-cyanosis-respiratory distress, bradycardia-tachycardia, poor skin color, arterial hypotension, irritability-lethargy-hypotonia, seizures, poor feeding, abdominal distention, metabolic acidosis, and hypo-hyperglycemia and/or some positive screening tests such as neutropenia, leukocytosis and high immature total ratio[10]. Suspected sepsis or unproven sepsis was diagnosed in the presence of clinical and laboratory findings described above without positive culture. Radiological findings were used to diagnose congenital pneumonia. Antibiotic treatment was administered with ampicillin and gentamicin for proven infection for 7 days until blood culture was reported.

Total and immature neutrophil values were compared with those of reference ranges taken from Manroe et al.[11], in relation to the time after birth when the blood samples were taken. Leukocytosis and leukopenia were defined if leukocyte count was >30,000/mm^3 and <5000/mm^3, respectively[12].

Informed consent was obtained from all families participating in the study. The study protocol was approved by the Hacettepe University Local Ethics Committee, Ankara, Turkey.

Blood Samples and IL-6, CRP, and PCT Measurements

Blood samples were collected in a red top Vacutainer blood collecting system and centrifuged, and the supernatant serum was stored at -20°C for IL-6 levels. The samples were studied by enzyme-linked immunosorbent test (Bender Medsystems®; Vienna, Austria), according to the manufacturer's instructions. Each sample was measured on a Bio-tech SERES® 900C instrument (Winooski, Vermont, USA). CRP determination was performed using Roche-Hitachi® 912 analyzer (Roche Diagnostics, Mannheim, Germany). PCT was measured by monoclonal immunoluminometric assay (Lumitest PCT, Brahm Diagnostica® GMBH, Berlin, Germany).

Statistical Analysis

Comparison between groups was done by t-test or Mann-Whitney U test, according to normal or abnormal distribution of data. Pearson correlation test was used for testing correlations. The ROC curves ('receiver operating characteristic' curve is the graphical plot of sensitivity and 1-specificity), area under curve and sensitivity/specificity tests were made on a personal computer using SPSS ® for Windows version 17. Sensitivity of a marker showed the power of positive prediction (true positives) of proven infection, and specificity of the marker was defined as predicting false-positives for proven infection (1-specificity) in this study population.

Results

This study involved 74 neonates (39 males, 35 females) with PPROM. Mean birthweight was 1734 ± 478 g (range: 730-2720 g), mean gestational age was 31.8 ± 2.5 weeks (range: 26-36 weeks), and duration of membrane rupture before delivery was 2-69 days (mean: 13.4 ± 15.2 days). Clinical chorioamnionitis was determined in 12 of all mothers (16%), and antenatal steroids were administered as at least one dose to 42 of 74 (56%) neonates.

Mean white blood cell count on the 1st day of life was 9716 ± 4955 mm^3 (range: 3300-59800 mm^3) and on the 3rd day was 8893 ± 4276 mm^3 (range: 4900-34500). Mean ratios of immature/mature (IM) and immature/total (IT) leukocytes of all infants on the 1st day were 0.239 ± 0.22 (range: 0.0-2) and 0.162 ± 0.12 (range: 0.0-0.6), respectively, and on the 3rd day were 0.210 ± 0.22 (range: 0.0-2) and 0.142 ± 0.16 (range: 0.0-0.6), respectively. Mean CRP levels on the 1st and 3rd day of life were found to be 0.49 ± 0.96 mg/dl (range: 0.01-4.7) and 0.88 ± 1.4 mg/dl (range: 0.01-7.30), respectively. Mean PCT levels on the 1st and 3rd day of life were 4.09 ± 6.4 ng/ml (range: 0.09-30) and 4.6 ± 8.5 ng/ml (range: 0.04-42.2), respectively. IL-6 level on the 1st day of life was 36.9 ± 58.4 pg/ml (range: 0.42-274.36). The clinical characteristics of the study population are summarized in Table I.

Thirty-two (43%) of 74 infants developed sepsis (Group 1), and 15 of these had positive blood culture (proven sepsis). Five of the infants with proven sepsis also had pneumonia, and 1 had urinary tract infection. Nine of 17 infants with suspected or unproven sepsis had pneumonia, 2 had meningitis, and 3 were diagnosed as urinary tract infection; the remaining 3 infants were unproven sepsis with clinical findings. Figure 1 provides the diagnoses of the infants. Forty-two (56%) of 74 infants did not show

Table I. Main Characteristics of Infants with PPROM (n=74)

Birthweight, g, mean (range)	1734 (730-2720)
Gestational age, weeks, mean (range)	31.8 (26-36)
Duration of rupture of membranes, days, mean (range)	13 (2-69)
Clinical chorioamnionitis, n (%)	12 (16)
Antenatal steroids, n (%)	42 (56)
Antenatal antibiotics, n (%)	68 (91)
Tocolytic therapy, n (%)	40 (54)
Hospitalization days (range)	8 (3-49)

PPROM: Preterm premature rupture of membranes.

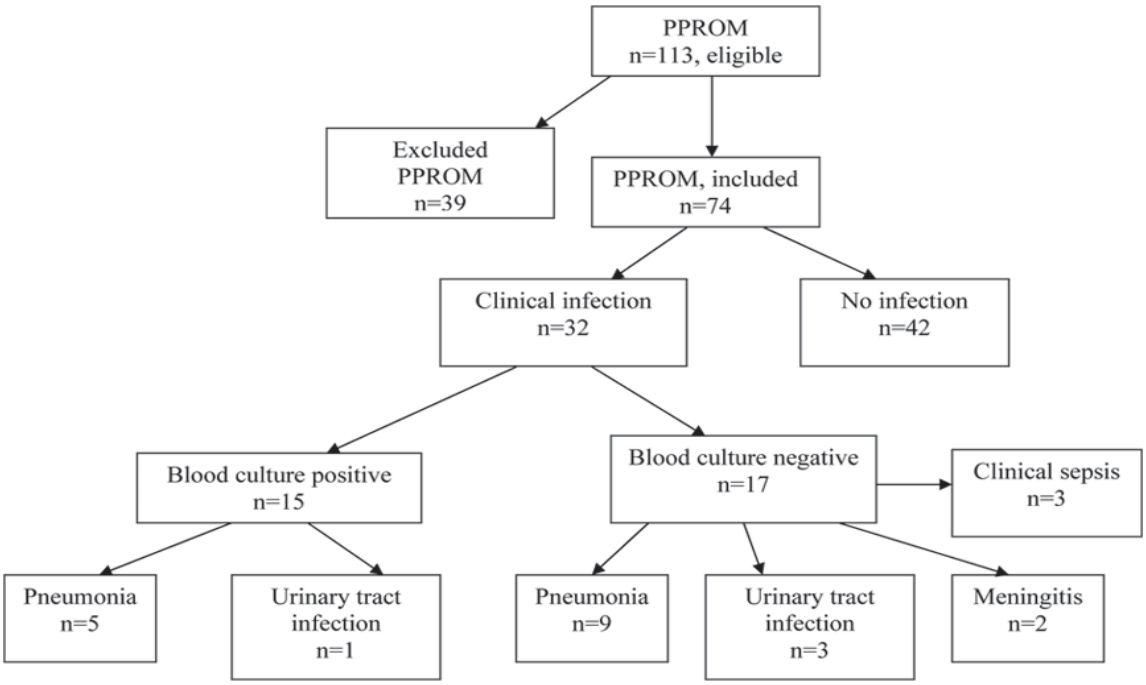

Fig. 1. Flow chart of infection in the study population.

clinical and laboratory findings of sepsis and constituted Group 2. Table II shows the clinical and laboratory findings of these groups.

There were no statistically significant differences between the two groups in birthweight (Group 1: 1667 ± 473 g, Group 2: 1793 ± 477; p=0.174), gestational age (Group 1: 31.4 ± 2.3 weeks, Group 2: 32.1 ± 2.8 weeks; p=0.299), duration of membrane rupture (Group 1: 14.2 ± 8.2 days, Group 2: 13.7 ± 9.1 days; p=0.839), and white blood cell count on the 1st (Group 1: 17700 ± 8530 mm^3, Group 2: 16500 ± 9250 mm^3; p=0.466) and 3rd (Group 1: 15400 ± 7885 mm^3, Group 2: 14900 ± 8610 mm^3; p=0.412) day of life. There were statistically significant differences between the two groups regarding IT ratio (Group 1: 0.21 ± 0.14, Group 2: 0.11 ± 0.05; p=0.01) and IM ratio (Group 1: 0.36 ± 0.38, Group 2: 0.14 ± 0.06; p=0.004) on the 1st day of life. There were also statistical differences between the two groups on the 3rd day of life for IT ratio (Group 1: 0.18 ± 0.13, Group 2: 0.09 ± 0.06; p=0.01) and IM ratio (Group 1: 0.30 ± 0.24, Group 2: 0.13 ± 0.05; p=0.003) of white blood cell count. There were significant differences between the two groups in 1st day CRP (Group 1: 0.85 ± 1.36 mg/dl, Group 2: 0.23 ± 0.25 mg/dl; p=0.016), 1st day PCT (Group 1: 7.2 ± 7.6 ng/ml, Group 2: 1.6 ± 4.0 ng/ml; p<0.001), 3rd day PCT (Group 1: 9.01 ± 11.5 ng/ml, Group 2: 1.34 ± 1.35 ng/ml; p=0.001), and IL-6 (Group 1: 80.7 ± 67.2 pg/ml, Group 2: 3.4 ± 3.5 ng/ml; p<0.001) levels. CRP levels were not different between Group 1 (1.2 ± 1.7 mg/dl) and Group 2 (0.58 ± 1.1 mg/dl) on the 3rd day of life (p=0.059) (Table II).

Correlation between chorioamnionitis and neonatal infection was statistically significant at 0.01 level, and Pearson correlation coefficient was found to be 0.311 and p=0.007.

Twenty-three infants developed respiratory distress syndrome and required surfactant. Necrotizing enterocolitis was diagnosed in 4 patients, 2 patients had chronic lung disease, 1 infant was treated for retinopathy of prematurity, and 4 infants were diagnosed with intracranial hemorrhage. Four infants in the study group died.

A cut-off point of 0.2 for IM leukocyte ratio on the 1st day of life showed 78% sensitivity and 69% specificity for neonatal infection. IT ratio of leukocytes had a cut-off point of 0.17, with 74% sensitivity and 54% specificity. CRP levels on the 1st day of life had a cut-off value of 0.72 mg/dl, with a sensitivity and specificity

Table II. Characteristics and Laboratory Results of the Patients with Sepsis (Group 1) and without Sepsis (Group 2)

	Group 1 n=32	Group 2 n=42	p
Birthweight, g, mean (range)	1667 ± 473	1793 ± 477	0.174
Gestational age, weeks, mean (range)	31.4 ± 2.3	32.1 ± 2.8	0.299
Duration of rupture of membranes (days)	14.2 ± 8.2	13.7 ± 9.1	0.839
1st day white blood cell count /mm^3	17700 ± 8530	16500 ± 9250	0.466
3rd day white blood cell count /mm^3	15400 ± 7885	14900 ± 8612	0.412
1st day immature/total ratio	0.21 ± 0.14	0.11 ± 0.05	0.01
3rd day immature/total ratio	0.18 ± 0.13	0.09 ± 0.06	0.01
1st day immature/mature ratio	0.36 ± 0.38	0.14 ± 0.06	0.004
3rd day immature/ mature ratio	0.30 ± 0.24	0.13 ± 0.05	0.003
1st day C-reactive protein (mg/dl)	0.85 ± 1.36	0.23 ± 0.25	0.016
3rd day C-reactive protein (mg/dl)	1.2 ± 1.7	0.58 ± 1.1	0.059
1st day procalcitonin (ng/ml)	7.2 ± 7.6	1.6 ± 4	<0.001
3rd day procalcitonin (ng/ml)	9.01 ± 11.5	1.34 ± 1.35	0.001
1st day interleukin-6 (pg/ml)	80.7 ± 67.2	3.4 ± 3.5	<0.001

of 56% and 58%, respectively. CRP levels on the 3rd day had a cut-off level of 0.78 mg/dl at 60% sensitivity and 63% specificity. PCT levels on the 1st day of life had a cut-off level of 1.74 ng/ml with 76% sensitivity and 85% specificity, and on the 3rd day of life, cut-off value for PCT was 1.8 with 89% sensitivity and 86% specificity. Statistical analysis revealed that the cut-off value of 7.6 pg/ml for IL-6 had 93% sensitivity and 96.7% specificity. ROC curves of parameters are shown in Figure 2 and cut-off values are listed in Table III.

Discussion

Early neonatal infection carries a high risk of morbidity and mortality. There is a serious dilemma for the neonatologist obliged to decide the necessity of administration of antibiotics[8]. Risk of neonatal infection after antibiotic prophylaxis remains significant, and administration of antibiotics is recommended shortly after birth in cases of PPROM[8,10,13]. All neonates with PPROM in our study had been administered peripartum antibiotics, which, combined with the limitations in standard diagnostic techniques for this age group, might explain the low rate of culture-confirmed sepsis[14].

Interleukin (IL)-6 is a cytokine that is produced by both T and B cells. It serves many functions including regulation of the host defense to infection. Exposure of the host to bacterial products results in a rapid and substantial increase in blood IL-6 concentrations. IL-6 in turn stimulates hepatocytes to produce acute phase reactants such as CRP[15]. PCT is the peptide prohormone of calcitonin, produced predominantly by monocytes and hepatocytes. Its circulating concentration increases within two hours of infection, and these markers (IL-6 and PCT) are the most extensively investigated acute phase proteins in neonatal sepsis and infections[15].

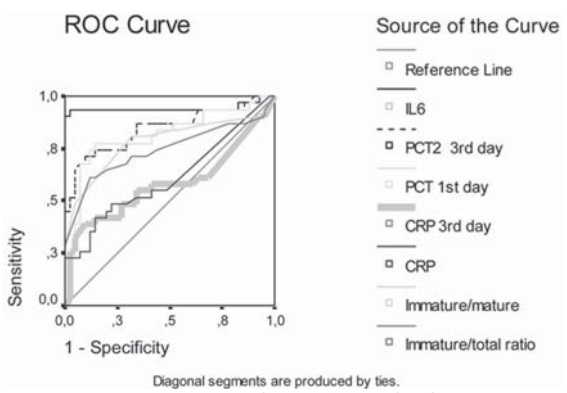

Fig 2. ROC curve for markers of infection.

Table III. Cut-off Values, Sensitivity and Specificity Levels of CRP, PCT and IL-6 for Proven Infection in Infants with PPROM

	Cut-off	Sensitivity %	Specificity %
1st day CRP	0.72 (mg/dl)	56	58
3rd day CRP	0.78 (mg/dl)	60	63
1st day PCT	1.74 (ng/ml)	76	85
3rd day PCT	1.8 (ng/ml)	89	86
1st day IL-6	7.6 (pg/ml)	93	96.7

CRP: C reactive Protein, PCT: Procalcitonin, IL-6: Interleukin 6.

Our results reveal that IL-6 concentration in neonates is a very sensitive, reliable and early marker of fetal inflammation and neonatal sepsis and can provide an accurate indication of whether a neonate will develop early sepsis, thus offering the opportunity for prompt diagnostic and aggressive therapeutic interventions. Of the pro-inflammatory cytokines, IL-6 has been one of the most widely studied for its potential as an infection marker in neonatal infection, but it is not a routine laboratory test among most intensive care units[15,16]. IL-6 has a complicated processing and is more expensive than other inflammatory markers. Our results are also similar to previous reports of highly significant differences in the concentrations of IL-6 in neonates with sepsis compared to those without sepsis[15-17]. Blood IL-6 concentrations and its polymorphisms have also been reported in neonates with periventricular leukomalacia[18,19], congenital pneumonia, necrotizing enterocolitis, or grade II–IV intraventricular hemorrhage[19,20]. In our study, the correlation of IL-6 concentrations with these neonatal complications was not possible due to the limited number of patients.

C-reactive protein (CRP) and PCT are the most important and widely used inflammation markers in neonatal intensive care units[15]. There are many studies focusing on inflammation and infection markers predicting sepsis and severe infections in neonates[5,8,14,21,22], but to our best knowledge, there has been no study aimed at testing these parameters in newborns with PPROM. CRP is also used widely as an inflammation and infection marker in neonates because it is cheap, easy and quick[15]. However, in our opinion, CRP is not as strong as IL-6 for predicting neonatal sepsis, as we observed in our findings, so this study aimed to test both CRP and PCT in comparison with IL-6. Early CRP levels within the 1st and 3rd day of life in our data seemed to be less sensitive and less specific than PCT. PCT has also been previously reported to discriminate between infected and non-infected newborns with a variable accuracy[23]. After the first promising report of Assicot et al.[24], further studies showed poor specificity of PCT[25,26]. High concentrations have been detected in several perinatal conditions such as preeclampsia, perinatal asphyxia, respiratory distress syndrome, and PROM[25,26]. However, we found greater sensitivity and specificity for PCT rather than CRP for infected neonates with a history of PPROM.

In conclusion, IL-6 is the best indicator of fetal inflammation and neonatal infection, providing an accurate indication immediately after delivery as to whether a neonate will develop early sepsis and offering the opportunity for prompt and aggressive diagnostic and therapeutic intervention. IL-6 in neonatal blood seems to be a sensitive marker for predicting early sepsis in preterm neonates with PPROM. This study shows that PCT is also a reliable marker for determination of early-onset infection. It is more sensitive than CRP and can be used widely since it is as cheap, easy and quick as CRP. We recommend determination of PCT levels in infants with PPROM at birth for early diagnosis of sepsis.

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