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Cord blood levels of cytokines as predictors of early neonatal sepsis

C Santana[1], MC Guindeo[2], G González[1], F García-Muñoz[1], P Saavedra[3] and E Doménech[4]

Neonatal Unit, Department of Pediatrics[1], Hospital Universitario Materno-Infantil de Canarias, Las Palmas de Gran Canaria; Clinical Laboratory, Hospital Dr. Negrín[2], Las Palmas de Gran Canaria; Department of Statistics[3], Universidad de Las Palmas de Gran Canaria; Department of Paediatrics[4], Hospital Universitario de Canarias, Santa Cruz de Tenerife

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Aim: To investigate whether cord blood levels of C-reactive protein, interleukin-1β, interleukin-6, interleukin-8, tumour necrosis factor-α and the soluble receptor of interleukin-2, are useful markers in the diagnosis of early neonatal sepsis. *Design:* Umbilical cord blood samples were obtained at birth from 261 neonates, but 5 of these newborns were excluded from the study. Group I included 10 newborns that developed early neonatal sepsis with a positive blood culture; Group II included 11 newborns with non-infectious perinatal diseases; Group III, which served as the control group, included 10 randomly selected patients, matched for gestational age, among the 235 healthy newborn babies. *Results:* There were no differences among the three study groups in levels of C-reactive protein, interleukin-1β, tumour necrosis factor-α and the soluble receptor of interleukin-2. Interleukin-6 was significantly elevated in Group I (360.4 ± 157.8 pg/ml) and Group II (158.8 ± 122.3 pg/ml), when compared with Group III (8.6 ± 3.12 pg/ml) ($p < 0.01$), whereas interleukin-8 was significantly elevated in Group I (389.3 ± 115.9 pg/ml) compared with Groups II (30.2 ± 5.1 pg/ml) ($p < 0.05$) and III (33.9 ± 8.6 pg/ml) ($p < 0.05$). A cut-off of 100.8 pg/ml for interleukin-6 obtained by the ROC (receiver operating characteristic) method gave a sensitivity of 50% and a specificity of 87%, and a cut-off of 111.7 pg/ml for interleukin-8 showed a sensitivity of 78% and a specificity of 91%.

Conclusion: While cord blood levels of interleukin-6 appear to be related to pathological conditions in the perinatal period (infectious and non-infectious), interleukin-8 seems to be a good predictor of early bacterial neonatal infection.

Key words: *Interleukin-1β, interleukin-6, interleukin-8, neonatal sepsis, soluble receptor of interleukin-2, tumour necrosis factor-α*

Candelaria Santana Reyes, Division of Neonatology. Department of Paediatrics, Hospital Universitario Materno Infantil de Canarias, Avenida Marítima del Sur s/n, ES-35016 Las Palmas de Gran Canaria, Spain (Tel. +34 928 444 694, fax. +34 928 444 775, e-mail. jesus.baezbaez@gobiernodecanarias.org)

Infectious diseases are an important cause of morbidity and mortality in the neonatal period. Among them, early sepsis is considered to be one of the most threatening conditions (1, 2). An early and accurate diagnosis leading to appropriate therapy would potentially ameliorate the final prognosis of these patients. Therefore, identifying tools for quick detection of early sepsis is a highly relevant goal in perinatal medicine.

There is increasing evidence that infection starts *in utero* in a significant number of neonates with early sepsis. Most are symptomatic within the first hours of life, and it has been proved that mothers with bacterial colonization and/or other infectious risk factors have a high probability of delivering babies with bacteraemia already present at birth (3).

Biologic parameters have been evaluated for the early diagnosis of neonatal sepsis. The most useful ones are white blood cell count (WBC), total number of neutrophils (TN), the immature to total neutrophils ratio (I/T) (4, 5) and the C-reactive protein (CRP) (6, 7). However, despite the number of tests available, none of them is absolutely reliable for an early and accurate diagnosis.

Several cytokines, such as IL-1β, IL-6, IL-8 and TNF-α, are important mediators in the host's systemic response to infection. High peripheral blood (PB) levels of these cytokines have proven useful in the diagnosis of early as well as late-onset neonatal sepsis (8–10). However, there is less known about the value of levels of cytokines in cord blood (CB) in identifying newborns that will develop early sepsis. In support of the role of cytokines in early sepsis, Miller et al. (11) reported an increase in levels of IL-6 in CB of newborn babies (32–42 wk gestational age) that developed infection, and Shimoya et al. (12) found an elevated level of IL-8 in CB in preterm foetuses (22–26 wk gestational age) with

Table 1. Characteristics of the study population.

	Group I	Group II	Group III
Male/female	3/7	6/5	4/6
Preterm/full term	5/5	4/7	5/5
Gestational age:mean (range) (wk)	36 (27–40)	37 (32–42)	37 (30–41)
Birthweight (g) (mean ± SD)	2595 ± 846.86	2840 ± 851.23	2531 ± 701.38
Babies with infectious risk factors	3	0	0

chorioamnionitis. More recent works (13, 14) have also found that IL-6 and IL-8 levels in CB could be useful in identifying the infected newborn.

We hypothesized that the combined measurement of cytokine levels in umbilical cord blood could be useful to establish an early and accurate diagnosis of sepsis. The main objective of this study was to determine whether the levels of IL-1β, IL-6, IL-8, TNF-α and soluble receptor of IL-2 (sIL-2R) in umbilical cord blood could be used to identify those newborns who will ultimately develop early neonatal sepsis. In addition, we evaluated whether the combined use of cytokine levels in CB and other standard tests (CRP, WBC, TN, I/T), improved the diagnostic accuracy of early sepsis over the use of any one single test.

Patients and methods

We collected CB samples from 261 newborn babies born in our hospital between June 1995 and May 1996, during routine staff work. All these newborns were followed-up clinically. Inclusion in study groups I, II and III was retrospective, after evaluation of the clinical status, and the laboratory and bacteriological data. A score for sepsis was used (15) that included the following clinical findings: "septic appearance" with poor perfusion or arterial hypotension, respiratory findings (respiratory distress, apnoea, cyanosis), neurological findings (irritability, hypotonia or lethargy), gastrointestinal findings (poor feeding, abdominal distension, or hepatomegaly) and early non-immunologic jaundice.

Five patients were excluded from the study because the diagnosis of sepsis could neither be proven nor ruled out. Ten newborns with proven sepsis were included in Group I, having at least two clinical findings, one or more abnormal laboratory findings, and a positive blood culture. Eleven newborns with non-infectious conditions were included in Group II, having normal laboratory results, negative cultures, and clinical findings consistent with diseases other than sepsis. The remaining 235 neonates did not exhibit any clinical or laboratory evidence of disease (infectious or non-infectious) during the first month of life, and were considered healthy. Among them, 10 newborns, matched for weight and gestational age, were randomly selected as controls, and constituted Group III.

Data including birthweight, gender, gestational age, form of delivery and the presence of infectious risk factors were collected for every newborn in the study (Table 1). Blood was drawn from the umbilical vein after birth, using a double clamp in the cord, and was collected in a silicone vacuum-filled tube. All samples were immediately centrifuged at 3500 rpm for 3 min. Aliquots of 50 µL were placed in plastic tubes, which were immediately frozen and stored at −70°C until analysed.

White blood cell values were scored according to the criteria proposed by Manroe et al. (4). CRP was measured by an immunoturbidimetric method (Tina-quan CRP, Boehringer-Maheim) according to the manufacturer's specification and was considered abnormal if higher than 1 mg/dl (16). WBC was performed in an automatic counter Coulter STKS (Coulter Electronics, Hialeah, Fla). Manual differential white cell counts were performed on Wright-stained blood slides. Standard criteria were used for recognition of the different cell subtypes (National Committee for Clinical Laboratory Standards on Cellular Morphology) (17).

Cytokines

IL-6, IL-8 and sIL-2R levels were measured using a chemoluminiscence enzymoimmunoassay in solid phase. Determinations were made with a completely automated analyser Immulite. The reagents and the analyser were supplied by "Diagnostic Products Corporation, Los Angeles (CA: 90045-5597)". IL-1β and TNF-α measurements were done manually by sandwich photometric immunoassay (ELISA, Boehringer Mannheim Biochemica), and were read with a microplate device (Whittaker). All samples were assayed in duplicate. Intra- and interassay variation coefficients were 3.29% and 3.87% for IL-6, 3.38% and 3.61% for IL-8 and 2.8% and 5.9% for sIL-2R, respectively. The detection limit was 1 pg/ml for IL-6, 6.2 pg/ml for IL-8 and 10 U/ml for sIL-2R. Intra- and interassay variation coefficients were 5.2% and 7.8% for IL-1β and 6.78% and 9.95% for TNF-α, respectively. The detection limit for IL-1β and TNF-α was 0.1 pg/ml.

Statistical analysis

Data are expressed as mean ± SEM, unless otherwise specified. The Mann-Whitney U test and the Kruskal-Wallis test were used to analyse differences among

Table 2. Diseases in Group II patients.

Disease	No. of patients
Meconium aspiration syndrome	1
Congenital heart defect	3
Intrauterine growth retardation	1
Polycythaemia	1
Pulmonary hypoplasia	1
Perinatal asphyxia	2
Hyaline membrane disease	1
Immunologic jaundice	1

groups, which were considered significant at $p < 0.05$. The degree of association between two variables was determined using the Pearson correlation coefficient. Receiver operating characteristic (ROC) curves were used to assess the diagnostic value of the tests. We performed a step study of all the variables based on a covariance analysis, followed by a discriminant analysis.

The study was approved by the Ethics Committee of the centre.

Results

Cord blood was collected from 261 newborn babies. Cytokines were measured in 31 babies (18 girls and 13 boys); 14 were preterm and 17 full-term newborns. Mean birthweight was 2645 ± 800.49 g (range 900–4090 g) and mean gestational age was 36.6 wk (range 27–42 wk). The characteristics of each group are presented in Table 1. We did not find any correlation between CB levels of CRP and cytokines and gestational age or mode of delivery.

Only three patients in Group I had infectious risk factors, and two of the mothers received intrapartum antibiotics in this group. None of them received antenatal steroid therapy. In Group I, group B streptococcus (GBS) was isolated in 9 samples, and type II *Haemophilus influenzae* in the remaining baby, who showed radiological findings consistent with pneumonia and cardiovascular failure. One baby with GBS infection had meningitis. All patients in this group survived. The diagnoses of the babies in Group II are presented in Table 2. Two patients died on days 3 and 4 because of pulmonary hypoplasia and a congenital heart defect, respectively. In all of these patients, infection was ruled out.

WBC, TN and I/T were not significantly different between babies with sepsis (Group I) and other groups (Groups II and III) (Table 3). In contrast, non-infected sick babies (Group II) had higher WBCs and TN than controls (Group III). The five patients in Group II with higher WBCs and TN were those whose mothers had received intrapartum oxytocin or had a very long labour. None of the patients in the study had neutropenia and the I/T index was similar for all three groups. Platelet counts were normal in all patients. The levels of CRP were similar for the three groups in this study (Table 3).

The CB levels of all the cytokines studied are shown in Fig. 1. There were no differences among the groups in IL-1β, TNF-α and sIL-2R values. Infants with early neonatal sepsis (Group I) had significantly higher levels of IL-6 and IL-8 than healthy infants (Group III). Babies with non-infectious conditions (Group II) showed levels of IL-8 similar to those of Group III babies. However, IL-6 levels were significantly elevated, in both Group I and II ($p < 0.05$) when compared to the control group (Group III).

IL-6 showed a specificity to identify infection of 87% at a cut-off value of 100.8 pg/ml, whereas the sensitivity was 50%, with a positive predictive value of 31% and a negative predictive value of 66%. IL-8 had the greatest ability to identify infected newborns, showing the greatest area under the ROC curve (0.79), while all other cytokines had areas closer to 0.5. The optimal decision level for IL-8 in cord blood was 111.7 pg/ml, with a sensitivity of 78%, specificity of 91%, a positive predictive value of 100% and a negative predictive value of 84%, for this cut-off point. The discriminant analysis concluded that the combined use of IL-8 with other cytokines or other variables such as CRP or leucocyte values did not improve its diagnostic capability.

Discussion

Our results suggest that the levels of IL-8 in CB are of diagnostic value in the identification of newborns that

Table 3. White blood cell count (WBC), total neutrophils (TN), immature to total neutrophils (I/T) ratio and C-reactive protein (CPR) in the study groups.

	Group I	Group II	Group III
WBC	$15\,050 \pm 3586$	$19\,420 \pm 6180$*	$13\,210 \pm 4376$
TN	9676 ± 2915	$11\,180 \pm 2735$*	7574 ± 2871
I/T ratio	0.07 ± 0.02	0.05 ± 0.03	0.09 ± 0.01
Platelets	$228\,000 \pm 46\,250$	$210\,700 \pm 54\,000$	$205\,800 \pm 57\,340$
CRP (mg/dl)	0.26 ± 0.37	0.10 ± 0.09	0.076 ± 0.12

* $p < 0.05$ vs control group (Group III).

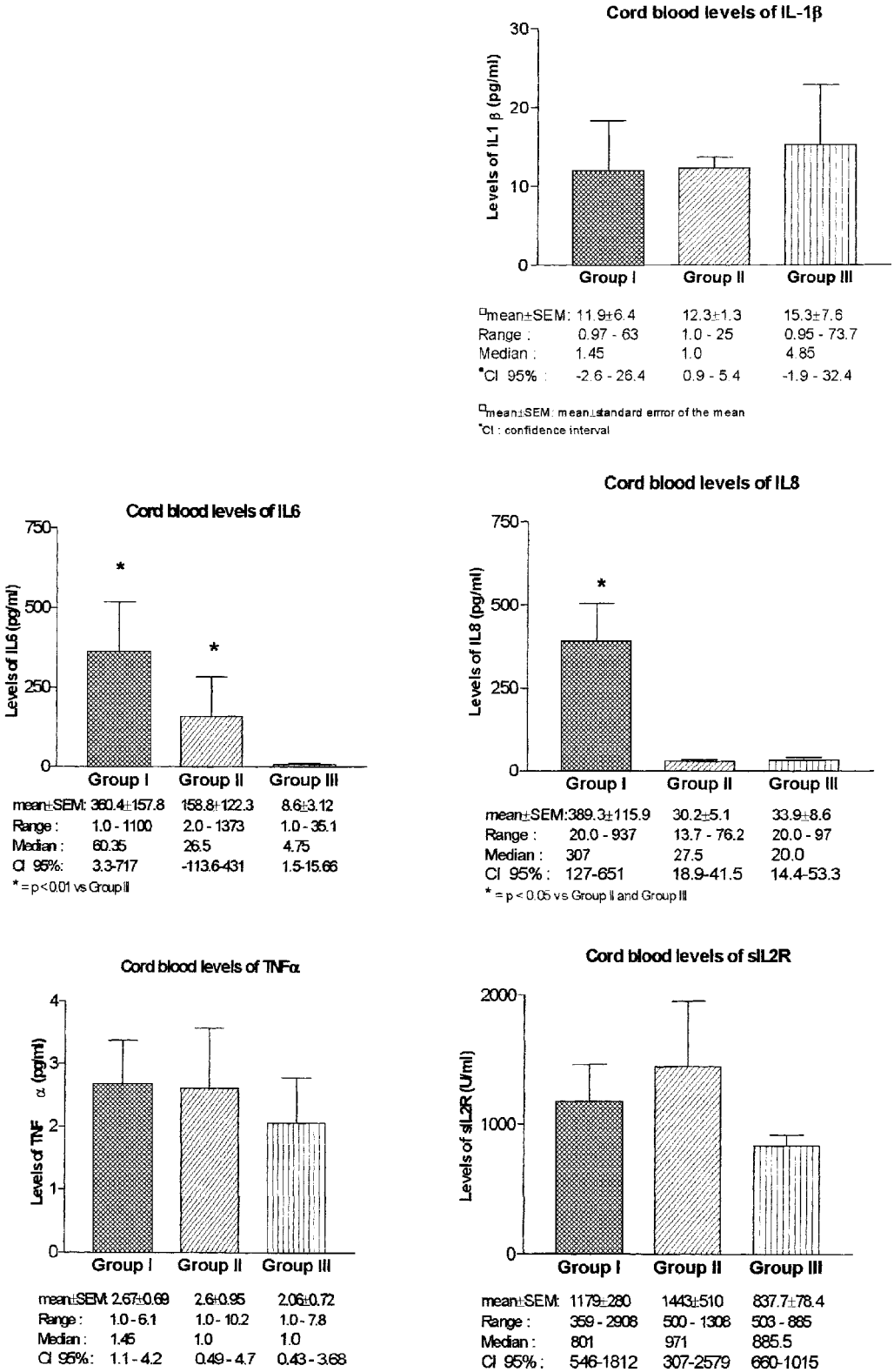

Fig. 1. Levels of interleukin (IL)-1β, IL-6, IL-8, tumour necrosis factor (TNF)-α and soluble receptor of interleukin-2 (sIL-2R) in the three groups of patients. There was no difference among groups in the levels of IL-1-β, TNF-α and sIL-2R. IL-6 levels were significantly higher in Groups I and II versus Group III. IL-8 was significantly elevated in Group I versus Groups II and III.

will develop early sepsis. Conversely, the value of IL-6 in identifying these infants is limited because it increases in the cord blood of neonates with infectious as well as non-infectious conditions. CRP, WBC, and the remaining cytokines in cord blood are not useful for this purpose.

CRP is an acute-phase reactant that does not pass the placenta, and the production of which does not vary with gestational age (18, 19). In our study, CRP levels in CB were not significantly different among groups. Our data are in accordance with those published by Rozansky et al. (20) and confirmed thereafter by others (19), who did not find the blood assessment of this acute-phase reactant of diagnostic value. Likewise, according to previous data (5) WBC, I/T and platelet counts are of no value in identifying the infected newborn.

Different studies have undertaken to examine the value of cytokines levels to establish the diagnosis of early sepsis (11–14, 21). Testing blood from the umbilical cord is less invasive and avoids the anaemization of tiny babies. It could allow early identification of infected newborns because its production is not modified by the form of delivery or non-infectious maternal conditions (12), nor is it correlated with maternal blood levels (22). Our study, as well as previous ones (10, 12, 23, 24), shows no correlation between cytokine levels in CB and gestational age.

There were no differences in IL-1 and TNF-α levels between study groups. Contrary to the results of Berner et al. (14), the levels found in our study were not elevated in patients who developed sepsis, In addition, Miller et al. (11) found elevated IL-1β levels in newborns with non-infectious diseases, compared with normal levels in newborns with infection. Contradictory results in PB have also been published. While some studies have shown significant elevation of both cytokines in neonates with sepsis (10, 23), others did not (25, 26). This disparity could again be due to the kinetics of these molecules, not completely understood in this early period of life, and because of the inhibitory power of IL-6 on TNF-α and IL-1β (at the transcription level and through stimulation of the synthesis of the IL-1β receptor antagonist and the TNF-α soluble receptor) (27).

To our knowledge, no studies have been conducted to evaluate sIL-2R levels in CB. We did not find any differences in the levels of this cytokine among the three study groups. In contrast, Spear et al. (28) found significantly elevated levels of sIL-2R in PB of infected preterm newborns.

IL-6 is a pleiotropic cytokine with several immunological functions, including induction of other acute phase reactants that play an important part in the host's response to infection and tissue damage. The role of this cytokine in the newborn, particularly during the first 24 h of life, is not well defined. Our results suggest that the level of IL-6 in CB could be related to different conditions in the neonatal period, whether infectious in origin or not. Some studies (29, 30) have found a decreased production of IL-6 in the neonate. Miller et al. (11) and Smulian et al. (31) found high levels of IL-6 in CB in newborns with infection compared with patients with non-infectious diseases. Lehrnbecher et al. (22) also found elevated IL-6 in CB and PB at 24 and 48 h of life in newborns with infection. Likewise, Messer et al. (32) found elevated levels of this cytokine during the first 12 h of life in infected newborns. The differences among these and our results could be related to the inclusion of a third group of sick neonates without infection (in which IL-6 is also significantly increased), because this circumstance modifies the results, lessening the diagnostic value of this cytokine. In accordance with our data, later studies have questioned the value of this cytokine to identify the infected neonate. Weeks et al. (33) found increased levels of IL-6 in the CB of newborns who went on to develop early sepsis, but also in patients with other non-infectious complications such as intracranial haemorrhage. Panero et al. (34) showed that during the first 24 h of life, IL-6 levels had a limited value for distinguishing babies with early sepsis from those with respiratory distress of non-infectious aetiology. The reasons for the different results in these studies could be the characteristics of the molecule (very short half-life, and kinetics largely unknown during this early period of life), and the different criteria used to include the infants in the groups for comparison. In our study, the diagnostic criteria were very strict, and those children that did not meet them were excluded from the study.

IL-8 is a chemotactic factor that acts on neutrophils that accumulate in the site of infection. Both placental cells and foetal monocytes/macrophages are able to increase its production after an infectious process originated in the uterus. The cord blood level of IL-8 appears to be a good predictor of early neonatal sepsis. Several studies have found early elevation of inflammatory markers in neonatal sepsis. In an elegant work by Shimoya et al. (12), it is shown that preterm foetuses with chorioamnionitis exhibit higher levels of IL-8 than non-infected foetuses. Likewise, Lehrnbecher et al. (22) and Berner et al. (14) found elevated levels of IL-8 in the CB of preterm and full-term newborns with documented early sepsis. Our results support those obtained by these authors and other studies on the PB of neonates with sepsis (8) and identify IL-8 as a diagnostic tool for early sepsis.

The main result of our work is the higher ability of IL-8 compared to CRP, IL-6 and other cytokines in the prediction or early diagnosis of infection. Levels of IL-8 in CB higher than 112 pg/ml seem to be useful in the identification of newborns that are likely to develop neonatal sepsis in the first few days of life, while IL-6 does not appear to be useful in the differentiation of neonates with infections and those with non-infectious pathological conditions.

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