Does Polycythemia Affect Interleukin-6 Response Pattern in Early Postnatal Period?

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Introduction: Neonatal polycythemia may result in increased cytokine production. We aimed to investigate whether polycythemia and partial exchange transfusion (PET) affect interleukin-6 (IL-6) response pattern in early neonatal period. **Methods:** Ninety-four newborns, 57 with polycythemia (Group 1) and 37 as control group (Group 2) were enrolled in the study. PET was performed at 4–6 hr following birth in the first group. Blood levels of IL-6 were measured at 2–4 hr following birth; measurements were repeated at 6 and 24 hr after PET in newborns with polycythemia and at similar hours in Group 2. In Group 1, two patients (3.5%) who were diagnosed with proven sepsis excluded from the study. **Results:** Both initial and the last IL-6 levels were higher in Group 1 (21.7; 5.5–190 pg/ml and 18.3; 2.7–92.4 pg/ml) than those of the

controls (8.4; 0.2–47.8 pg/ml and 8.6; 2.0–21.0 pg/ml) ($P = 0.001$ for both comparisons). In Group 1, IL-6 levels increased at 6 hr after PET and decreased thereafter. IL-6 showed the same pattern in the control group. IL-6 levels were higher than >70 pg/ml in two (3.6%), seven (12.7%), and two (3.6%) subjects during three evaluation steps, respectively. Neither clinical nor proven sepsis was subsequently detected in any of these subjects. IL-6 levels were within the acceptable values in Group 2. **Conclusion:** IL-6 levels seem to be high in newborns with polycythemia during the first days of life, although they rarely exceed maximum acceptable levels. The pattern of IL-6 response might be taken into account to optimize its use in the diagnosis of early-onset neonatal sepsis. *J. Clin. Lab. Anal.* 24:340–347, 2010. © 2010 Wiley-Liss, Inc.

Key words: Interleukin-6; newborn; polycythemia; partial exchange transfusion; sepsis

INTRODUCTION

The reported incidence of neonatal polycythemia in term newborns varies from 0.4 to 12% (1–3). Red blood cell concentration is the primary determinant of blood viscosity in the newborn (2); therefore, polycythemia results in increased blood viscosity and this may result in impaired tissue perfusion. Hence, this condition requires urgent diagnosis and prompt management. Relationship between viscosity and hematocrit (Hct) is almost linear up to an Hct of 65% and exponential thereafter. Because instrument to measure viscosity is not readily available in most neonatal intensive care units (NICU), hyperviscosity is usually suspected in the presence of suggestive symptoms and an abnormally high Hct (4).

Polycythemia rubra vera (PV) represents a clonal hematological disorder defined by an abnormal expansion of erythroid precursors and megakaryopoiesis, in particular. It was reported that the cytokines might be responsible from the proliferation of normal and neoplastic megakaryocytes. There are two studies done

on adults on this subject in the medical literature. Wickenhauser et al. are the first to describe spontaneously expression of IL-6 and IL-6R by PV megakaryocytes and point toward fundamental regulatory alterations of the IL-6 synthesis of this disease (5). In 2002, Hermouet et al. showed that both IL-11 and IL-8 are also overproduced in PV, apparently by bone marrow stromal cells (6). To the best of our knowledge, there has been no study measuring IL-6 levels in neonatal polycythemia. Therefore, we aimed to investigate whether polycythemia and partial exchange transfusion (PET) affect IL-6 response pattern in early neonatal period.

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SUBJECTS AND METHODS

Setting

This prospective observational study was conducted in the busy NICU of Zekai Tahir Burak Maternity Teaching Hospital which was a level III hospital in Turkey. The study period was determined from October 2008 to September 2009.

Subjects

Study subjects

In our NICU, there is a routine screening program for neonatal polycythemia in infants at high risk for polycythemia (small for gestational age (SGA), large for gestational age (LGA), born to diabetic or pre-eclamptic mothers, monochorionic twins especially the larger twin, and infants with morphological growth restriction) as suggested (7,8). Any infant with clinical features suggestive of polycythemia, including respiratory distress, tachypnea, hypoglycemia, lethargy, irritability, apnea, seizures, jitteriness, vomiting, weak sucking reflex, poor feeding, and cyanosis, were also examined for polycythemia.

According to our NICU protocol, at approximately 2–4 hr of life a heel stick Hct is obtained from these newborns and a venous sample for spun Hct is obtained whenever the heel stick Hct exceeds 70%, neonatal polycythemia is then defined whenever the venous Hct exceeds 65%. Each infant recognized as having neonatal polycythemia is carefully examined and observed for potential symptoms of polycythemia and screened as well for hypoglycemia (whole blood glucose <50 mg/dl). PET was performed in symptomatic babies with an Hct greater than 65% or in asymptomatic babies with an Hct greater than 70%. In practice, the PET is performed at approximately 6 hr of age, using normal saline (0.9 g/100 ml). The volume to be exchanged was calculated based on the observed and desired Hct (<60%) [volume to be exchanged = infant's blood volume $\times$ (observed Hct–desired Hct)/observed Hct] (3).

Exclusion criteria

Exclusion criteria from the neonatal history were conditions which possibly affect acute phase response including predisposing to sepsis (maternal fever, urinary tract infection, chorioamnionitis, early rupture of membranes (PROM) >18 hr), perinatal asphyxia, Apgar score <6 at 5 min, cardiovascular or respiratory failure, and major birth defects. The subjects whose blood sampling could not be performed according to the protocol design were also excluded.

Groups

Group 1

All the newborns were visited by a fellow in neonatology while they were in Department of Obstetrics beside their mothers. The risky newborns were investigated for polycythemia with the same criteria and they were admitted to the NICU if PET would be performed.

During the study period, initially, 127 infants were proved to be polycythemia and PET was required in 84 of them (66.1%).

Twenty-seven out of 84 had at least one of the exclusion criteria.

Therefore, 57 infants were included in the study. At the end of the study, two infants dropped from the study because of proven sepsis following PET.

Finally, 55 infants (29 females and 26 males) were evaluated for the study group.

The study subjects were investigated for polycythemia because of the following risks:

- SGA: 22 (40%)
- LGA: 3 (0.54%)
- Maternal diabetes: 6 (10.9%)
- Maternal preeclampsia: 10 (18.1%)
- Symptomatic infants: 53 (96.3%)
- Twin birth (larger infant): 5 (0.09%)

As shown, some of the infants had two or more risk polycythemia.

Group 2

Thirty-seven healthy newborns (15 male 22 female) visiting the Department of Obstetrics with their mothers were consecutively recruited in order to serve as a control group. They were of gestational age and gender matched with the study group, although their birth weights were bigger than those of the study subjects. Some of the infants needed to be evaluated for polycythemia because of the following risks:

- SGA: 9 (24.3%)
- LGA: 5 (13.5%)
- Maternal diabetes: 2 (0.54%)
- Maternal preeclampsia: 1 (0.27%)

However, they were not defined as polycythemia according to the above-mentioned criteria. All were asymptomatic and not admitted to the NICU.

Perinatal and neonatal characteristics

All perinatal data were collected prospectively and included maternal age, preexistent or pregnancy-related diseases, and mode of delivery. Neonatal data included

gestational age, birthweight, grouping for birthweight and gestational age, premature birth (<37 weeks), gender, delayed cord clamp, twin-to-twin transfusion, genetic disorder, and length of hospital stay. Gestational age was based on the last menstrual period, on ultrasonographic determinations between 8th and 14th week of gestation and on the Ballard test in cases of unknown gestational age. SGA, appropriate for gestational age, LGA, and twin-to-twin transfusion was diagnosed based on previously defined criteria (9–11). Delayed cord clamp (>3 min after birth) was described according to the obstetrician's report.

METHODS

Blood Samples

Blood samples were collected from peripheral vein for performing hematological data at 2–4 hr following the birth in both groups. Simultaneously, blood was collected to heparinized microcapillaries (110 mm length and 1–2 mm internal diameter) for venous Hct measurement.

Blood levels of white blood cell (WBC), Hct, platelet (PLT), IL-6 were measured at 2–4 hr following birth; measurements were repeated at 6 and 24 hr after PET in newborns with polycythemia and at similar hours in controls. To exclude sepsis, C-reactive protein (CRP) values were detected in both groups.

Blood cultures were taken before and 24 hr after PET. Blood samples were immediately transported to the laboratory and processed upon arrival.

Blood Count

WBC and PLT were measured via automated blood analysis unit (Micros 60 Analyzer, ABX Diagnostics, Montpellier, France). It was known that spun Hct values were higher than values obtained by the Coulter counter method and showed a better correlation with viscosity (7,12–15). Therefore, the Hct values was measured using centrifugation at 10,000–15,000 rounds per minute for 3–5 min of capillary tubes (CENTRIC 150, Železniki, Slovenia).

Determination of plasma levels of IL-6

Plasma levels of IL-6 were analyzed by IL-6 solid phase, enzyme labeled, chemiluminescent sequential immunometric assay on IMMULITE 1000 analyzer, according to the manufacturer's instructions (Siemens Diagnostic Product Corporation, Los Angeles, CA). Cut-off value was accepted as 70 pg/ml (16).

Determination of serum levels of CRP

Serum concentrations of CRP were measured by a Tinaquant CRP (Latex) high sensitive immunoturbidimetric

assay on the Roche Modular P analyzer according to the manufacturer's instructions (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany). Cut-off value was accepted as 10 mg/l (16).

The samples were blinded to the technician to avoid bias.

Statistics

SPSS 17.0 (SPSS, Chicago, IL) was used for statistical analysis. Data were expressed as the arithmetic mean $\pm$ standard deviation or median (minimum–maximum), according to the distribution of the data. Differences among the groups were tested using independent *t*-test or Mann–Whitney *U*, as appropriate. Chi-square test was used for categorical data. The relationships between the Hct and IL-6 levels were investigated by Spearman rank correlations. The level of significance was set at 0.05 in all comparisons.

Ethics

The study was performed with permission from the local Ethics Committee of Zekai Tahir Burak Maternity Teaching Hospital, Turkey. The blood samples were collected after taking informed consent from all parents.

RESULTS

Demographic and clinical characteristics of the study subjects are shown on Table 1. Although birth weight was bigger in Group 2, gestational age and sex distribution were not different between the groups. The most common presenting symptom was hypoglycemia ($n = 26$, 47.3%) in Group 1 (Table 2). The rate of indirect hyperbilirubinemia requiring phototherapy was higher in Group 1 ($n = 13$, 23.6%) than that of Group 2 ($n = 3$, 8.1%), although not significantly ($P = 0.10$).

The results of hematologic parameters during the study period are shown in Table 3.

Both initial and the last median IL-6 levels were higher in Group 1 (21.7; 5.5–190 pg/ml and 18.3; 2.7–92.4 pg/ml) than those of the controls (11; 0.5–58 pg/ml and 8.4; 0.2–47.8 pg/ml) ($P = 0.001$ for both comparisons). In Group 1, IL-6 levels increased 6 hr after PET and decreased thereafter. IL-6 showed the same pattern in the control group (Fig. 1). IL-6 levels were higher than >70 pg/ml in two (3.6%), seven (12.7%), and two (3.6%) subjects during three evaluation steps, respectively. Neither clinical nor proven sepsis was subsequently detected in any of these subjects. IL-6 levels were not higher than this cut-off value in Group 2.

Initial Hct values were significantly correlated with simultaneously detected IL-6 levels ($P = 0.001$, $r = 0.45$) (Fig. 2). The correlation between the last Hct and IL-6 levels was also significant but weak ($P = 0.02$, $r = 0.24$).

TABLE 1. Demographic and Clinical Characteristics of All Newborns According to the Groups

	Group 1 (<i>n</i> = 55, 59.8%)	Group 2 (<i>n</i> = 37, 40.2%)	<i>P</i> value
Maternal age (mean ± SD)	28.2 ± 7.2	30.2 ± 3.0	0.06
Maternal disease, <i>n</i> (%)			
Preeclampsia	10 (18.2)	1 (2.7)	0.04
Gestational diabetes	6 (10.9)	2 (5.4)	0.46
Cesarean delivery, <i>n</i> (%)	40 (72.7)	30 (81.1)	0.50
Gestational age, week (mean ± SD)	37.3 ± 2.1	37.1 ± 2.0	0.61
Birth weight (g), (mean ± SD)	2,459 ± 669	2,827 ± 767	0.01
Birth weight group, <i>n</i> (%)			
SGA	22 (40.0)	9 (24.3)	
AGA	30 (54.5)	23 (62.1)	
LGA	3 (5.5)	5 (13.5)	0.06
Male gender, <i>n</i> (%)	26 (47.2)	15 (40.5)	0.67
Premature birth, (<37 weeks), <i>n</i> (%)	21 (3.8)	17 (45.9)	0.59
Delayed cord clamp, <i>n</i> (%)	11 (20.0)	0 (0.0)	0.003
Twin-to-twin transfusion, <i>n</i> (%)	5 (9.1)	0 (0.0)	0.08
Genetic disorder, <i>n</i> (%)			
Trisomy 21	2 (3.6)	0 (0.0)	0.51
Length of hospital stay, (median, range)	4 (2–34)	2 (2–10)	0.001

TABLE 2. Symptoms and Complications Related to Polycythemia

	<i>n</i> = 55 (%)
<i>Symptoms, n</i> (%)	
Hypoglycemia	26 (47.3)
Tachypnea	14 (25.5)
Feeding intolerance	13 (23.6)
Hyperbilirubinemia	13 (23.6)
<i>Complications^a, n</i> (%)	
Thrombocytopenia (<150 × 10 ³ /mm ³)	16 (29.1)
Necrotizing enterocolitis	1 (1.8)

^aTwo subjects who were diagnosed to be sepsis were excluded from the study.

Both initial and the last median CRP levels were higher in Group 1 (1.0; 0.05–13.6 mg/l and 3.2; 0.1–37.9 mg/l) than those of the controls (0.4; 0.2–3.1 mg/l and 1.7; 0.4–7.9 mg/l) ($P = 0.01$ and $P = 0.007$). In Group 1, CRP levels steadily increased throughout the study period in both groups (Fig. 3). There was no correlation between Hct and CRP values. CRP values were higher than 10 mg/l in two (3.6%), two (3.6%), and four subjects (7.3%) during three evaluation steps, respectively. Neither clinical nor proven sepsis was subsequently detected in any of these subjects. CRP levels were below the higher acceptable value of 10 mg/l in Group 2.

Blood culture was not taken from the control subjects. These infants were discharged from the hospital with their mothers without any problems. Blood cultures were taken before and after PET in the study group. No grew was reported in first blood cultures. However, clinical sepsis developed in two subjects. Subsequently, coagulase negative *Staphylococcus epidermitis* was isolated from the blood cultures. Data of these infants

were not analyzed in the study as their acute phase reactant levels were high owing to sepsis. Neither clinical nor proven sepsis was subsequently detected in any of the analyzed subjects.

DISCUSSION

Underlying causes of neonatal polycythemia include (1) increased fetal erythropoiesis; placental insufficiency (secondary to preeclampsia or chronic renovascular diseases), endocrine abnormalities associated with increased fetal oxygen consumption resulting in fetal hypoxia, congenital thyrotoxicosis, maternal diabetes with poor glycemic control, and genetics disorders (e.g., trisomy 13, 18, and 21); (2) hypertransfusion; and delayed cord clamping (>3 min after birth), gravity (position of the delivered infant before cord clamp), twin-to-twin transfusion syndrome owing to vascular communication, intrapartum asphyxia (blood flow is shifted from the placenta to the fetus) (15). In this study, maternal diseases, including preeclampsia and gestational diabetes, were more common among infants with polycythemia. Delayed cord clamp was considered in 11 subjects. Five subjects with polycythemia were defined as having twin-to-twin transfusion syndrome.

As previously mentioned, the etiopathogenesis of PV is different from neonatal polycythemia. In PV, there is a clonal hematological disorder defined by an abnormal expansion of erythroid precursors and megakaryopoiesis, in particular. It was reported that the cytokines might be responsible for the proliferation of normal and neoplastic megakaryocytes (5). To our knowledge, there is no study investigating the influence of cytokines on neonatal polycythemia. Therefore, we investigated

TABLE 3. Comparison of Hematological Parameters Between the Groups During the Study Period^a

	Group 1 (n = 55)	Group 2 (n = 37)	P value
White blood cell ($\times 10^3/\text{mm}^3$) (median, range)			
At 2–4 hr	17.1 (6.0–43.2)	21.5 (9.9–29.1)	0.004
At 6 hr	17.1 (7.1–42.7)	19.0 (8.9–25.0)	0.31
At 24 hr	14.5 (5.6–39.1)	14.5 (5.6–39.1)	0.001
Hematocrit (%) (mean $\pm$ SD)			
At 2–4 hr	71.8 $\pm$ 3.1	57.7 $\pm$ 4.8	0.001
At 6 hr	60.4 $\pm$ 4.3	53.3 $\pm$ 4.6	0.001
At 24 hr	58.3 $\pm$ 4.6	53.9 $\pm$ 5.1	0.001
Platelet ($\times 10^3/\text{mm}^3$) (mean $\pm$ SD)			
At 2–4 hr	178 $\pm$ 55	261 $\pm$ 70	0.001
At 6 hr	172 $\pm$ 62	254 $\pm$ 63	0.001
At 24 hr	165 $\pm$ 69	253 $\pm$ 48	0.001
Interleukin-6 (pg/ml) (median, range)			
At 2–4 hr	21.7 (5.5–190)	8.4 (0.2–47.8)	0.001
At 6 hr	23.0 (1.0–257)	11.0 (0.5–58.0)	0.001
At 24 hr	18.3 (2.7–92.4)	8.6 (2.0–21.0)	0.001
C reactive protein (mg/l) (median, range)			
At 2–4 hr	1.0 (0.05–13.6)	0.4 (0.2–3.1)	0.004
At 6 hr	2.1 (0.2–32.2)	1.3 (0.07–6.9)	0.01
At 24 hr	3.2 (0.1–37.9)	1.7 (0.4–7.9)	0.007

^aAt 2–4 hr following birth, at 6 hr following birth, 24 hr after partial exchange transfusion in the study group (group 1) and the same hours in the control group (group 2).

Fig. 1. Boxplot graphic showing interleukin-6 pattern in both groups; at 2–4 hr following birth, at 6 hr following birth, 24 hr after partial exchange transfusion in the study group (Group 1) and the same hours in the control group (Group 2).

whether there was a relation between IL-6 and Hct levels in infants with polycythemia.

It is known that IL-6 is an important mediator of host response to stress and infection. Although previous studies found that inflammatory cytokines including IL-6 were released in uninfected infants with perinatal

Fig. 2. Scatter plot graphic of the correlation between hematocrit (Hct) and interleukin-6 (IL-6) in all subjects at 2–4 hr following birth.

complications, the results obtained to date remain discordant (17,18). Chiesa et al. (17) showed that the diagnostic value of IL-6 at birth might be altered by the physiologic severity and risk indexes. In adult patients with septic or cardiogenic shock, the authors found that IL-6 concentrations were increased in both patient populations. In rodents, catecholamines and epinephrine in particular have been shown to increase IL-6

Fig. 3. Boxplot graphic showing C-reactive protein (CRP) pattern in both groups; at 2–4 hr following birth, at 6 hr following birth, 24 hr after partial exchange transfusion in the study group (Group 1) and the same hours in the control group (Group 2).

production (19). Chiesa et al. (17) reported that IL-6 values observed in the delivering mothers and in their babies at all three neonatal ages were negatively associated with gestational age. De Jongh et al. (20) also found that neonatal IL-6 levels were weak and negatively correlated with the duration of gestation, and these higher IL-6 concentrations in near-term healthy neonates might be the result of subclinical perinatal infections, which were frequent with preterm labor, although none of these babies became symptomatic or received antibiotic treatment. On the contrary, Zhou et al. (21) stated that there was no reason to believe that near-term infants would have been more prone to mistaken assignment of healthy status than term infants born in the same clinical conditions. They thought that preterm delivery could be more stressful for the unprepared fetus, which could induce an increase in serum IL-6, probably via the stimulation of IL-6 production by adrenal gland cells. We did not show that the levels of IL-6 were different in the premature infants compared with the levels in the term neonates at 2–4 hr of life, suggesting different physiologic processes.

Although it was shown that Apgar score had a significant effect on babies' IL-6 values at birth (17), the data available on the role of IL-6 in the injury response to hypoxia ischemia or asphyxia are currently limited. The infants with low Apgar score were not included in the study.

IL-6 is an early marker of neonatal sepsis. In the medical literature, the cut-off values for IL-6 to diagnose sepsis have ranged from 18 to 70 pg/ml

(16,22). In this study, we investigated whether IL-6 and CRP response were influenced by polycythemia in neonates without sepsis for the first few days of life. We chose a high cut-off value of 70 pg/ml to clearly identify whether IL-6 increased owing to sepsis or not. In this study, when this cut-off value was chosen, two infants whose clinical findings and blood culture results were consistent with sepsis were excluded from the study as IL-6 increase was not related to polycythemia alone. Among analyzed polycythemic infants, IL-6 levels were higher than >70 pg/ml in two (3.6%), seven (12.7%), and two (3.6%) subjects during three evaluation steps, respectively. Neither clinical nor proven sepsis was subsequently detected in any of these subjects. We commented that higher IL-6 values might be related with polycythemia in these infants as they had no other perinatal complications which could increase IL-6.

There are limited data on the influence of antibiotic therapy on the time course of IL-6. Lannergård et al. (23) investigated the accuracy of using body temperature, serum amyloid A (SAA), CRP, and IL-6 in the work-up for early or late step-down therapy after an initial course of intravenous cefuroxime. They observed that the time course of SAA and CRP during the first 24 hr, in patients with sepsis with a short duration of illness but without septic shock, showed increasing levels during the initial course of intravenous therapy. However, body temperature and IL-6 decreased, regardless of illness duration. The authors reported that beyond 24 hr, all four biomarkers declined, again regardless of the duration of illness. In this study, the infants with polycythemia were given prophylactic antibiotic after PET. No antibiotic treatment was given to control subjects. Although IL-6 levels were higher in patient group than those of the controls at all evaluation steps, they showed the same pattern in both groups.

As a cytokine, IL-6 is the major inducer of hepatic protein synthesis including CRP. Previous studies have sought to identify which pre and perinatal complications would mimic or mask alterations in the CRP response caused by infection, but they have yielded conflicting results (17). Kushner et al. (24) found that maternal fever during labor or delivery, PROM, perinatal asphyxia, and other problems not resulting from infection are associated with increased CRP in umbilical cord blood. Ainbender et al. (25) identified fetal distress, low 1 min Apgar score, gestational diabetes, maternal drug addiction, maternal fever, and PROM as confounding factors in the diagnosis of early-onset neonatal infection. Schouten-Van Meeteren et al. (26), however, did not observe differences in CRP concentrations between perinatally asphyxiated infants and a control group at 12–24 hr after birth. According to Chiesa et al.'s study, at birth, CRP was significantly lower than

at 24 and 48 hr of life. PROM (>18 hr), perinatal distress, and gestational hypertension significantly affected the neonatal CRP dynamics, but at specific ages. Forest et al. (27) also showed that CRP was increased in those with a history of PROM, fetal distress, or chorioamnionitis. In this study, the infants with low Apgar scores, with a history of PROM, fetal distress, or chorioamnionitis were not included as we aimed to exclude the factors which possibly influence the acute phase response.

CRP is a late and specific marker of neonatal sepsis. To define sepsis, CRP cut-off values established by Chiesa et al. were 5.0 mg/l at birth, 14.0 mg/l at 24 hr, and 9.7 mg/l at 48 hr of life (17). Haque (16) suggested the cut-off value of CRP as 10 mg/l or >2 SD above normal value for diagnosis of NS. To exclude sepsis, we chose the 10 mg/l in early postnatal period. According to this cut-off value, two infants whose clinical findings were consistent with sepsis were excluded from the study. These infants were treated for sepsis and subsequently coagulase negative *Staphylococcus epidermitis* grew in blood cultures. Among analyzed polycythemic subjects, CRP values were higher than 10 mg/l in two (3.6%), two (3.6), and four subjects (7.3%) during three evaluation steps, respectively. Neither clinical nor proven sepsis was subsequently detected in any of these subjects. CRP levels were below the higher acceptable value of 10 mg/l in control subjects. We thought that higher IL-6 subsequently resulted in higher CRP in these infants.

Jancovic et al. (28) compared changes of serum CRP concentrations in neonates with proven neonatal sepsis in response to initial antibiotic therapy (inappropriate or appropriate). They showed that in patients with non-adequate initial antibiotic therapy of neonatal sepsis serum CRP concentrations increased further during the second day of treatment. By contrast, the use of appropriate antibiotic therapy in the same time period followed the significant decrease of serum CRP levels in their patients. In this study, CRP response pattern was similar in both groups. Although the newborns in patient group were given prophylactic antibiotic treatment, sepsis was not diagnosed in any of the studied subjects.

Management strategies for polycythemia include both supportive and specific therapy. A PET is the only specific therapy for polycythemic infants with hyperviscosity syndrome. Dempsey et al. (29) reported that there was no evidence of long-term benefit from PET in polycythemic infants, and the incidence of gastrointestinal injury was increased and the long-term outcome was more likely to be related to the underlying cause of polycythemia. In this study, two infants were excluded from the study because of proven sepsis (culture

positive) with markedly increased acute phase response developed following PET. At the final evaluation of 55 infants, the complications observed were thrombocytopenia, indirect hyperbilirubinemia, and necrotizing enterocolitis.

In 1986, a longitudinal profile of immunologic parameters was investigated in burned patients with specific reference to clinical criteria (resuscitation, plasma exchange, surgical excisions, and sepsis) by Stratta et al. (30). They found that plasma exchange and surgical excision and grafting procedures were characterized by multiple serologic changes and improvement in lymphocyte function. Similarly, although there are studies investigating acute phase response for sepsis evaluation after exchange transfusion (31,32), we did not find any study on IL-6 and CRP response pattern following PET. In this study, we observed that IL-6 levels increased at 6 hr after PET and decreased thereafter, whereas CRP levels steadily increased throughout the study period. We could not compare the study subjects with polycythemic, but PET was not performed owing to ethical reasons. It is a fact that comparison of two groups is needed to determine whether these changes on IL-6 and CRP are related or not with PET.

Furthermore, it was reported that several cytokines—IL-6, IL-11, granulocyte-monocyte colony-stimulating factor, and thrombopoietin—could regulate PLT numbers and functions in humans (33). PLTs, often considered acute phase reactants, might also be influenced by these cytokines. It was previously shown that serum IL-6 and CRP were elevated in reactive thrombocytosis. In adults, it is speculated that defects in the regulation of IL-6 synthesis take part in the pathogenesis of primary polycythemia, often called PV, and occur when excess red blood cells are produced as a result of an abnormality of the *bone marrow*. Wickenhauser et al. (5) described for the first time an abnormally raised IL-6 production by PV megakaryocytes in this disease. Hermouet et al. (6) showed that both IL-11 and IL-8, two cytokines known to affect erythropoiesis, were overproduced in PV. However, there is no study on IL-6 response in neonatal polycythemia.

Our study has several limitations. First, the number of the subjects is small. Second, it would be better if more homogeneous patient group having similar etiopathogenesis (e.g., increased fetal erythropoiesis) for neonatal polycythemia could be selected to evaluate the relation between IL-6 and polycythemia. However, this study is important for being the first one in this area. We showed that although IL-6 levels were high in infants with polycythemia they rarely exceeded maximum acceptable levels. We believe that a larger study and analysis of the cytokines may aid in the generation of a cytokine profile in neonatal polycythemia before and after PET. The pattern

of IL-6 response might be taken into account to optimize its use in the diagnosis of early-onset neonatal sepsis.

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