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Research Article

Cord Blood Interleukin-6 is a Predictor of Respiratory Morbidities in Preterm Neonates

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Abstract

Background: Inflammation is central to premature baby respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). IL6 is a widely distributed collection of enzymes that are principally involved in the turnover of membrane phospholipids and lipid digestion. They are also important for the inflammation pathways because they are the first step in the production of eicosanoids and other inflammatory mediators. It has a dual role because it contributes to the inflammation route and is also the key enzyme engaged in surfactant degradation. To investigate the effect of IL-6 concentration as a predictor of the development of respiratory distress (RDs) and bronchopulmonary dysplasia (BPD) in premature infants.

Methods: The research was carried out at Ain Shams University's Obstetrics and Gynecology Hospital's Labor and Delivery ward and NICU from 12 January 2012 to 28 June 2013. The study involved 95 premature newborns born at less than 34 weeks of gestation. They were split into two groups based on whether they suffered from respiratory distress or not.

The study excluded preterm infants with substantial congenital malformations, inborn errors of metabolism, chromosomal abnormalities, and risk factors for neonatal sepsis, such as premature rupture of membranes, Maternal UTI, Chorioamnionitis, and Rh hemolytic illness.

All patients had a full history taken. On admission, a full clinical examination and laboratory investigations were performed. Blood samples were drawn from the maternal side of the cut end of the umbilical cord for the measurement of serum interleukin 6 (IL-6) levels, radiological investigations, and neonatal follow-up until discharge.

Results: RDS and BPD infants had significantly greater IL-6 concentrations than preterm controls ($P < 0.05$ and $p < 0.01$, respectively).

Conclusion: High levels of IL6 in preterm newborn cord blood independently predict the development of RDS and BPD.

Keywords: *Interleukin 6; Respiratory Distress Syndrome; Bronchopulmonary Dysplasia; Preterm Infant; Cord Blood*

Introduction

Inflammation is a key factor in premature baby respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD). Although elevated cytokine concentrations in the blood or amniotic fluid during pregnancy promote lung maturation and prevent the postnatal development of RDS, they may also trigger the development of BPD [1].

In postnatal plasma and tracheal aspirates from preterm infants with RDS, both inflammatory cytokines and lipid mediator levels are elevated, and even more so in infants with BPD [2].

A pleiotropic cytokine called interleukin-6 (IL-6) affects several systems, including the respiratory system, in addition to playing a function in inflammation and the immunological response. Reports on the function of IL-6 in pulmonary pathophysiology have multiplied rapidly in recent years. Lung epithelial cells also produce IL-6 in response to different stimulants, such as allergens and respiratory viruses [3]; it was found to be increased in bronchoalveolar lavage fluid (BAL) in mice infected with *Streptococcus pneumoniae* or *Mycoplasma pneumoniae* [4] and in the lung tissue of septic rats. Lung epithelial cells also produce IL-6 in response to different stimulants, such as allergens and respiratory viruses.

Aim of the Study

The aim of this study was to determine the role of interleukin-6 (IL-6) concentration as a predictor for the development of respiratory distress (RDs) and bronchopulmonary dysplasia (BPD) in preterm infants.

Methods

This study was conducted at the Ain Shams University's Obstetrics and Gynecology Hospital's Labor and Delivery ward and NICU from 12 January 2012 to 28 June 2013. The study involved 95 premature newborns born at less than 34 weeks of gestation. They were divided into 2 groups; study and control groups according to whether they developed respiratory distress or not.

The study group: 37 preterm neonates who developed respiratory distress proved by clinical and radiological findings.

The control group: 58 preterm neonates who were admitted to the NICU but did not develop RDS, also proved by clinical and radiological findings.

Exclusion criteria:

The following preterm baby population was excluded:

1. Major congenital abnormalities.
2. Inborn errors of metabolism.
3. Chromosomal abnormalities.
4. Risk factors related to neonatal sepsis e.g., premature rupture of membranes (PROM), Maternal UTI, and Chorioamnionitis.
5. RH hemolytic disease.

All studied neonates were subjected to the following:

1. Complete history taking with special emphasis on Maternal medical history including D.M., hypertension, pre-eclampsia 1st day of last menstrual period for gestational age assessment Antenatal history including maternal intake of steroids, history suggestive of congenital infection, PROM, or maternal fever. Natal history including mode of delivery and delivery room intervention.

Recorded Apgar scores at one minute and five minutes after birth.

2. Thorough clinical examination including Gestational age assessment using the Ballard scoring system. Birth weight, crown heel length, and occipitofrontal circumference and correlation with centiles. Complete examination including cardiac, abdominal, neurological, skeletal, chest, and respiratory examination searching for congenital malformation and manifestations of respiratory distress.

3. Laboratory investigations were done on admission:

a. CBC with a differential count.

b. CRP with titre.

c. Blood gases analysis.

d. Blood samples were withdrawn from the maternal side of the cut end of the umbilical cord for the measurement of concentrations of serum interleukin 6 (IL-6) by ELISA technique.

4. Calculation of oxygenation index on admission for those who were ventilated:

$$\text{Oxygenation Index} = \frac{F_iO_2 \times MAP}{P_aO_2}$$

Where: $Fi0_2$ = flow of inhaled oxygen (%).

MAP = Mean airway pressure ($cm.H_20$).

$Pa0_2$ = arterial partial pressure of oxygen (Torr).

5. Radiological investigations:

Chest X-ray was done to:

a. Prove or exclude RDS.
b. Determine the grade of RDS.
c. Determine the development of BPD.
6. Follow up of the neonates.

Preterm neonates were followed up till discharge to determine the following:

a. Duration of 0_2 therapy
b. Duration of CPAP
c. Duration of mechanical ventilation
d. Duration of hospital admission
e. Mortality.

Statistical analysis of data using the SPSS Program.

Analytical methods

1. **Specimen collection:** Umbilical cord blood was obtained from the umbilical cord vein within 15 minutes after birth. The blood was collected into a heparinized glass tube and immediately centrifuged; the plasma was stored under -70c until analysis.
2. **Determination of cord blood IL-6:** The quantitative determination of IL-6 was done using commercially available ELISA kits.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using the SPSS program (Statistical Package for Social Sciences) software version 20.

Descriptive statistics were done for numerical parametric data by mean, standard deviation, and minimum and maximum of the range and for numerical nonparametric data by median and 1st and 3rd interquartile range, while they were done for categorical data by number and percentage. Analytical analyses were done for quantitative variables using a t-test in cases of two independent groups with parametric data and the Mann-Whitney U test in cases of two independent groups with non-parametric data.

Correlations were done using the Spearman rank correlation test for numerical nonparametric and categorical data. Analytical analyses were done for qualitative data using the Chi-square test for parametric variables. The level of significance was taken at P value < 0.05 is significant, otherwise non-significant.

Results

Our study showed that the RDS group had significantly lower birth weight and gestational age compared with the control group and showed that APGAR scores at 1 min. and 5 min. were significantly lower in the RDS group. The number of mothers who took steroids before delivery was significantly higher in the control group compared with the RDS group. The RDS group had significantly higher (duration of O_2 therapy, duration of CPAP, duration of mechanical ventilation) compared with the control group.

		Groups		T-test	P-value
		Group I RDS (N = 37)	Group II Control (N = 58)	2.811	0.006*
IL-6	Range	10,000 - 500,000	75,000 - 500,000	- 4.236	< 0.001*
	Mean ± SD	246.251 ± 186.600	148.250 ± 151.004		

Table 1: *Cord blood IL-6 markers of the studied groups.*

**Significant, RDS: Respiratory Distress Syndrome; IL-6: Interleukin-6.*

Table 1 showed IL-6 level was significantly lower in the control group compared with the RDS group.

There was a significant increase in the number of patients who developed BPD, NEC, and PDA in the RDS group compared with the control group. Also, mortality and duration of hospital stay were significantly higher in the RDS group.

The BPD group had significantly lower gestational age and birth weight compared with the non-BPD group.

	BPD				T-test	P-value
	Yes		No			
	Mean	SD	Mean	SD	T-test	P-value
IL-6	500.000	0.000	164.689	134.404	7.413	<0.001*

Table 2: *Comparison between BPD and non-BPD as regards cord blood markers.*

**Significant, Cord blood markers (IL-6).*

Table 2 showed that there was a significant increase in levels of IL6 in BPD groups compared with the non-BPD group.

There was a significant negative correlation between IL-6 and (GA and BW).

Also, there was a significant positive correlation between IL6 and duration of 0_2 therapy, duration on CPAP, duration of mechanical ventilation, and duration of hospital stay.

The graph shows the AUC for IL-6 to diagnose RDS.

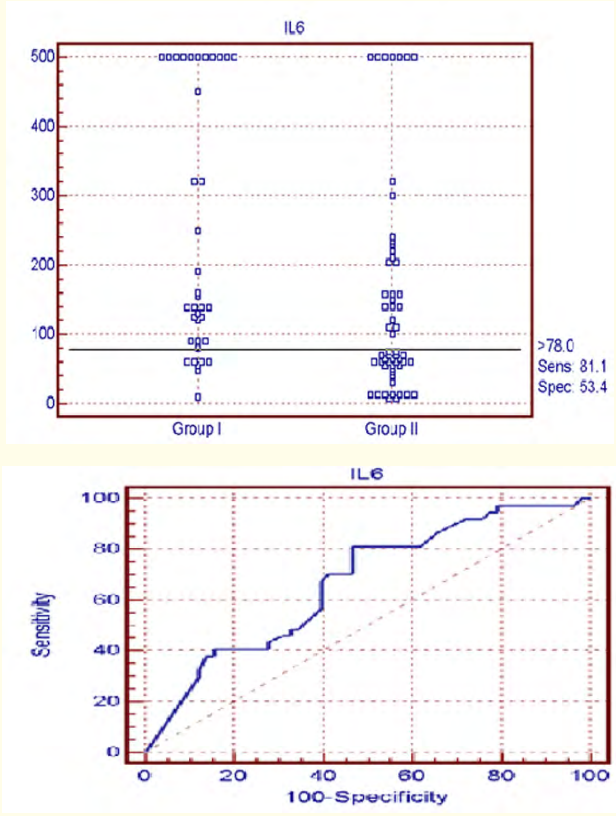

Figure 1: *Show scatter curve, cut point, sensitivity, and specificity of IL6 to diagnose RDS.*

The figure 1 showed that the level of IL6 at the cutoff point >78 µg/L can diagnose RDS with sensitivity = 81.1%, specificity = 53.4%, positive predictive value = 52.6%, negative predictive value = 81.6% with accuracy = 66.9%

The graph shows AUC for IL6 to predict BPD.

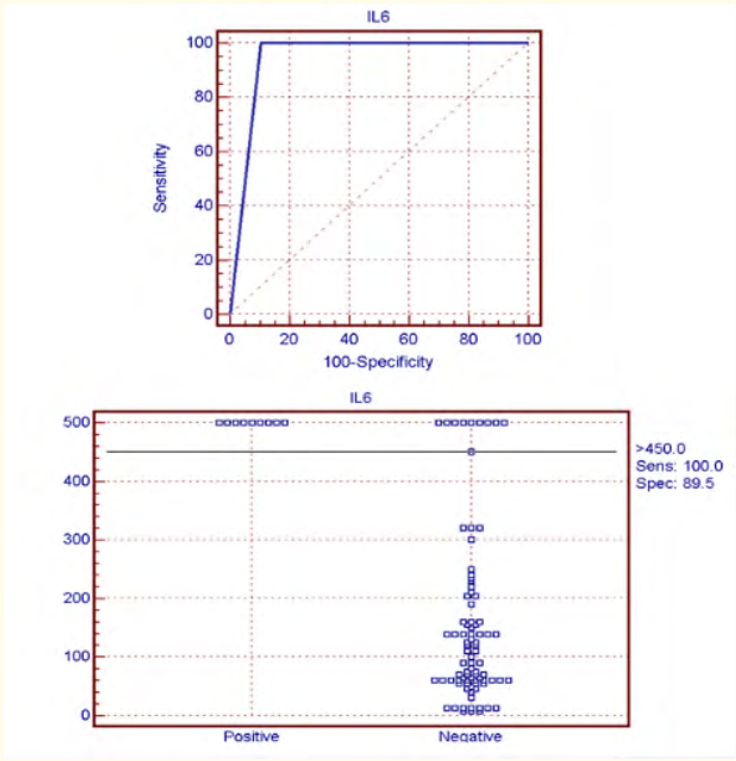

Figure 2: *Show scatter curve, cut point, sensitivity, and specificity for IL6 to predict BPD.*

Figure 2 showed that the level of IL6 at the cutoff point > 450 µg/L can predict BPD with sensitivity = 100%, specificity = 89.5%, positive predictive value = 50%, negative predictive value = 100% with accuracy = 94.8%.

Discussion

Respiratory distress syndrome (RDS) occurs predominantly in premature infants. The condition is characterized by signs of respiratory distress and increasing oxygen requirements shortly after birth as a consequence of surfactant deficiency [5], bronchopulmonary dysplasia (BPD) was originally described as a complication of respiratory distress syndrome (RDS) and included the influence of 3 key factors: lung immaturity, acute lung injury, and disordered repair of the original lung injury [6]. Inflammation, contributed to by antenatal (chorioamnionitis) and postnatal (local or systemic infections, hyperoxia, ventilator-induced injury) factors, initiates and modifies the process of lung injury in the developing lung [7]. Given the multifactorial aetiopathogenesis of BPD involving diverse molecular signaling pathways, a variety of biomarkers detected in different biological fluids have been proposed for early identification of infants predisposed to BPD [7].

IL6 is a widely distributed group of enzymes primarily implicated in the turnover of membrane phospholipids and lipid digestion. It is also crucial for the inflammation pathways, as it is the first step to produce eicosanoids and other inflammatory mediators, it has a dual role, as it contributes to the inflammation pathway, and it is also the main enzyme involved in the catabolism of surfactant. We aim to determine the role of IL-6 concentration as a predictor for the development of respiratory distress (RDs) and bronchopulmonary dysplasia (BPD) in preterm infants. The infants with RDS in our study were born at earlier GA (mean, 31.8 wks.; range, 28 - 34 wks.) than those infants without RDS (mean, 33.1 wks.; range, 30-34 wks.; $P < 0.001$).

We demonstrated a significant increase in cord blood IL6 in the RDS group compared with the control group and in the BPD group compared with the non-BPD group. This may be explained by the fact that it is one of the numerous factors that contribute to pulmonary inflammation and it could include a systemic inflammatory response that may induce preterm birth and the postnatal development of BPD [1]. Yoon., *et al*. found that neonates in whom bronchopulmonary dysplasia developed had a significantly higher median IL-6 concentration in umbilical cord plasma at birth than did those in whom bronchopulmonary dysplasia did not develop [9]. This association remained significant after adjustment for gestational age at birth, indicating that the development of a systematic foetal inflammatory response syndrome is a risk factor for the occurrence of chronic lung disease [8].

Our study showed that the level of IL6 at the cutoff point > 78 µg/L can diagnose RDS with sensitivity = 81.1%, specificity = 53.4%, positive predictive value = 52.6%, negative predictive value = 81.6% with accuracy = 66.9%.

Also, it showed that the level of IL6 at the cutoff point > 450 µg/L can predict BPD with sensitivity = 100%, specificity = 89.5%, positive predictive value = 50%, negative predictive value = 100% with accuracy = 94.8%.

Also, Yoon., *et al*. constructed a ROC curve to identify the occurrence of BPD and found that cord plasma IL-6 concentration of 25 pg/ml had a sensitivity of 68% and a specificity of 74% [9].

One limitation of our study was that the number of preterms who developed BPD was relatively small and the use of more sophisticated statistical analysis, such as logistic regression, was, therefore, not possible.

We concluded that in preterm infants, cord blood IL-6 may serve as an early marker for the development of RDS and BPD. The advantage of this measure is that cord blood provides an easily obtainable marker of lung injury in the preterm infant and that cord blood IL-6 predicts the development of RDS and BPD with very high sensitivity. IL-6 measurement may aid in the decision whether to start early treatment, on the first day of life with exogenous surfactant.

Inflammation plays a central role in respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) in the preterm infant. Although antenatally increased concentrations of cytokines in the blood or amniotic fluid stimulate lung maturation and prevent the postnatal development of RDS, they may also initiate the development of BPD.

Postnatally, both inflammatory cytokines and lipid mediator levels are increased in plasma and tracheal aspirates from preterm infants with RDS, and even more so in infants with BPD.

The present study was designed to evaluate the use of cord blood IL-6 concentrations to predict the development of respiratory distress syndrome and bronchopulmonary dysplasia in preterm newborns.

The study included 95 preterm neonates ≤ 34 weeks of gestation. They were divided into study and control groups according to whether they developed respiratory distress syndrome and bronchopulmonary dysplasia or not.

All patients were subjected to adequate history taking, full clinical examination, CBC, CRP, ABG, and measurement of cord blood IL-6 concentration at birth.

In our study, patients who developed RDS had significantly lower GA and birth weight compared with those who did not develop RDS.

IL-6 was significantly higher in the RDS group compared with the control group.

Also, patients with BPD had significantly higher IL-6 compared with patients who did not develop BPD.

There was a significant negative correlation between IL-6 and G.A, B.W.

Our study also revealed that IL-6 at the cutoff point > 450 µg/L can predict BPD with sensitivity = 100%, specificity = 89.5%, positive predictive value = 50%, negative predictive value = 100% with accuracy = 94.8%.

Conclusion

In conclusion, high IL-6 levels in cord blood from preterm infants independently predict the development of RDS and BPD and may serve as an early biomarker for this disease. We speculate that high cord blood levels of IL-6 in preterm infants reflect early lung injury, which contributes to RDS severity and progress toward BPD.

We also concluded that in preterm infants, cord blood IL-6 may serve as an early marker for the development of BPD. The advantage of this measure is that cord blood provides an easily obtainable marker of lung injury in the preterm infant and that cord blood IL-6 predicts the development of BPD with very high sensitivity. IL-6 measurement may aid in the decision whether to start early treatment, on the first day of life with exogenous surfactant.

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