EVALUATION OF SOLUBLE E-SELECTIN AS A MARKER FOR NEONATAL SEPSIS

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ABSTRACT

ur aim was to evaluate the diagnostic value of soluble E-selectin "sE-selectin" in comparison with commonly used markers for identification of neonatal sepsis (C-reactive protein "CRP", total leukocytic count "TLC", absolute neutrophil count "ANC", immature to total neutrophil ratio "I/T ratio") and to assess its prognostic value. Newborn infants in whom clinical sepsis was suspected were eligible for the study. A full sepsis screen was performed. CBC, CRP, and sE-selectin were measured. The optimal cutoff value for each marker was calculated. The sensitivity, specificity, predictive values, and likelihood ratios for each test and combination of tests for predicting neonatal sepsis were also determined. Forty-five newborn infants with suspected clinical sepsis were investigated. Twenty-nine infants were proved to be infected by bacterial cultures and 16 were found to be non-infected. Control group included 15 healthy newborn infants. Plasma sE-selectin levels were significantly higher in infected infants (156.9 \pm 77.0 ng/ml) compared with non-infected (88.8 \pm 47.1 ng/ml) and control groups (86.7 \pm 37.4 ng/ml) (p < 0.0001). Infants with Gram negative sepsis had significantly higher sE-selectin levels than those with Gram positive sepsis (P=0.04). Neither gestational age nor the onset of sepsis (early vs. late) influenced sE-selectin levels in infected infants. The optimal cutoff values for prediction of sepsis were sEselectin: 130 ng/ml; CRP: 8.0 mg/l; and I/T ratio ≥ 0.2. Plasma sE-selectin levels had a sensitivity of 59% and a specificity of 87% in prediction of neonatal sepsis. CRP performed best as diagnostic test for neonatal sepsis, with an overall sensitivity and specificity of 86% and 97%, respectively. Performing sE-selectin with either CRP or I/T ratio increased the specificity but reduced the sensitivity of the tests for the diagnosis of neonatal sepsis. Plasma sE-selectin levels were higher in non-survivors than in survivors (p=0.03) and those with hemodynamic dysfunction than in those without hemodynamic dysfunction (p=0.01). We conclude that plasma sE-selectin levels were elevated in neonatal sepsis. Higher levels were found in those with Gram negative sepsis compared with those with Gram positive sepsis. Gestational age and onset of sepsis did not influence sE-selectin levels in infected neonates. Plasma sE-selectin had low diagnostic value when used alone or in combination with other tests, however, it can be used as a prognostic indicator in neonatal sepsis.

INTRODUCTION

The morbidity and mortality from neonatal sepsis continues to be a major

problem. Early warning signs and symptoms are often non-specific, subtle, and can easily be confused with non-infective causes. The timely diagnosis of



neonatal sepsis is critical because the illness can be rapidly progressive and in some instances fatal.² As microbiological culture results are not usually available until at least 48-72 hours after the specimen reaches the laboratory, early identification of infected cases is recognized as a major diagnostic problem in newborn infants. Thus, a reliable infection marker or a set of markers are required to promptly and accurately identify the infected cases so that treatment can be started without delay. Equally difficult is the exclusion of infection in infants with suspected sepsis, as continuation of broad-spectrum antibiotics for presumptive bacterial infection frequently leads to unnecessary treatment and also the possibility of emergence of multi-resistant organisms.

Hematological and biochemical markers such as I/T ratio.³⁻⁶ platelet count,³ CRP, ^{4.5.7.8} various cytokines, ⁹⁻¹² procalcitonin^{8,13} and neutrophil CD64¹⁴ have all been suggested as being useful indicators for early identification of septic infants. All of these studies have yielded conflicting results, and the satisfactory solutions remain to be found.

E-Selectin is expressed by the endothelium after activation at sites of acute inflammation and is significant in neutrophil and some T-cell migration to the site of injury.15 It takes part in the first step of the 'adhesion cascade', the 'rolling of leukocytes', leading to the extravasation of the white cells to the sites of inflammation, infection or damage, it is uniquely displayed only on endothelium and is almost exclusively inducible.16 In human diseases in which unchecked inflammation contributes to the pathogenesis of disease process, soluble forms of E-Selectin "sEselectin" are elevated, and the elevations have been interpreted as indicating a role for the molecules in the pathogenesis of inflammation, as well as indicating the magnitude of inflammatory response. 17,18 For this reason, sE-selectin is considered early and reliable marker of the immune

activation and response. Moreover, sEselectin has been reported to be a reliable marker of infection and sepsis in adults. ¹⁹⁻²¹ Soluble E-selectin have been studied to a lesser extent in neonatal sepsis. ^{10,22,23}

The aims of this study were:

- 1) to assess plasma levels of sE-selectin levels in newborn infants with sepsis 2) to determine whether changes in sEselectin levels are dependent on gestational age, onset of sepsis, or Gram stain of the organism
- 3) to establish the diagnostic utilities (sensitivity, specificity, predictive values and likelihood ratios of sE-selectin in comparison to commonly used laboratory markers for sepsis (CRP, I/T ratio, TLC, ANC), both individually and in combination, for early diagnosis of neonatal sepsis; and
- 4) to test whether sE-selectin levels have any prognostic value in neonatal sepsis.

SUBJECTS AND METHODS

Study population

Newborn infants with suspected clinical sepsis in the neonatal intensive care unit at Mansoura University Children's Hospital during the period between July 2002 and February 2003, were eligible for study. Clinical sepsis was defined as the presence of three or more of the following categories of clinical signs derived from a validated sepsis score:²⁴

- (a) temperature instability (hypothermia, hyperthermia);
- (b) respiratory (grunting, intercostal retractions, apnea, tachypnea, cyanosis);
- (c) cardiovascular (bradycardia, tachycardia, poor perfusion, hypotension):
- (d) neurologic (hypotonia, lethargy, seizures):
- (e) gastrointestinal (feeding intolerance, abdominal distension).

Classification of infants included in the study

Three groups were prospectively defined: Group 1: The infected group consisted of 29 infants who had been confirmed as septicemic from positive blood cultures. Group 2: The non-infected group consisted of 16 infants who met the initial screening criteria for suspected clinical sepsis but were subsequently found not to have positive bacterial cultures in blood, cerebrospinal fluid or urine specimens; radiological evidence of pneumonia or nercotizing enterocolitis; and the infant continued to improve after antibiotic treatment was stopped.

Group 3: The control group consisted of blood samples taken from 15 well, newborn infants for CBC, CRP, and sEselectin measurements.

METHODS

Collection and processing of plasma specimens

Plasma samples were centrifuged at 1000 Xg within 30 minutes of collection and were stored at -70°C until analysis was done, with the exception of the samples for CRP which were analyzed immediately.

CBC, TLC, ANC and I/T ratio

Complete blood cell counts in specimens were performed in an automatic counter (Abbott Cell-Dyn 1700 Hematology Analyzer, Abbott laboratorics, USA) and differential counts were performed manually on Wright-stained blood slides.

CRP assay:

Plasma CRP concentrations were measured using an immunoturbidimetric method (Human Diagnostics, Wiesbaden, Germany) and was quantified by means of an autoanalyzer Hitachi 911. According to the manufacturer, the detection limits of the assays for CRP was 0.1 mg/L. Reference values for healthy neonates, using quantitative techniques, are less than 1.6 mg/dl during the first two days of life, and less than 1 mg/dl for the remainder of the neonatal period.²

sE-selectin assav

Plasma concentrations of sE-Selectin were assayed by sCD62E ELISA kit (Diaclone Research, Besacon, France). This technique uses a monoclonal antibody specific for E-selectin that has been precoated onto the wells of microtiter strips. Standards, samples, and a human control are placed into the wells, followed by a polyclonal antibody specific for E-selectin, conjugated to horseradish peroxidase. After removal of the unbound conjugated antibody, substrates for horseradish peroxidase were added and the product was quantified using a spectrophotometer at 450nm, with a correction by subtraction of background absorbance at 650 nm. A standard curve was plotted and sE-selectin concentrations were determined by interpolation from the curve. The sensitivities of the assays were <0.5 ng/ml, the intraassay coefficient of variance averaged 6.4%, and the interassay coefficient of variance was 4.1%.

STATISTICAL ANALYSIS

Values are given as means \pm SD, median (range), or as the number of subjects and proportions. One-way ANOVA test and Independent samples Student- t test were used for group comparisons of normally distributed variables, and the Kruskal-Wallis test and Mann-Whitney U test were used for comparisons of variables with skewed distribution. The Chi-square test was used to compare proportions.

The receiver operator characteristic (ROC) method was used to determine the best possible cutoff values for sE-selectin, CRP, I/T ratio as predictors of neonatal sepsis; the curves were obtained by plotting sensitivity on the y axis against the false positive rate (1-specificity) on the x axis for all possible cutoff values of the tests. From these curves, the best or optimal cutoff value for each biochemical test was determined. Regarding TLC, ANC and platelet counts we used the following cutoff values: TLC $(<5000/mm^3; or >$ $20,000/\text{mm}^3;^{7,25}\text{ANC}$ ($<2000 \text{ or } >7500/\text{mm}^3$ ²⁶ and Platelet count (<150,000/mm³). ²⁶ The sensitivity, specificity, predictive values and likelihood ratios were worked out using the optimal cutoff values, to allow the selection of the best combination of tests for the diagnosis of neonatal sepsis. For the purpose of this study, a combination of tests was judged positive if any one of the selected markers exceeded their respective optimal cutoff values. Statistical significance was determined at p < 0.05 and all p-values reported in this study are of the two-sided type. All statistical tests were performed by SPSS for Windows Release 10.0.1, SPSS Inc., Chicago, IL, U.S.A.

RESULTS

Classification and basic characteristics

The clinical characteristics of the study groups are summarized in table 1. There were no significant differences between gestational age, birth weight, gender, postnatal age at blood sampling between the three groups. Forty-five neonates with suspected clinical sepsis were investigated. In twenty-nine neonates suspected infection were confirmed, of which 21 (72.4%) were due to Gram negative, 8 (27.6%), were due to Gram positive organisms, respectively; 9 infants (31.0%) had early onset sepsis, and 20 infants (69.0%) had late onset sepsis.

Detailed accounts of the organisms are summarized in table 2. Klebsiella pneumonia was the commonest organism (41.3%) isolated from blood cultures followed by Pseudomonas auerogenosa (13.8%), Staphylococcus aureus (10.3%), Eschereschia coli (10.3%), Methicillin resistant Staphylococci (6.9%), Coagulase negative Staphylococcus (6.9%), Serratia marscens (3.4%), Enterobacter spp.(3.4%) and Streptococci Fecalis (3.4%). In 16 neonates (non-infected group) infection was excluded by negative bacterial and fungal cultures.

Laboratory markers of sepsis in the studied groups

Plasma sE-selectin, CRP, I/T ratio in the infected group were significantly increased when compared with the corresponding values of the non-infected group (p<0.0001, for all). Likewise, plasma sE-selectin, CRP, I/T ratio in the infected group were significantly higher than in the control group (p<0.0001; for all). In contrast, no significant differences were detected between the non-infected group and controls (p>0.05). No significant differences were found between groups regarding TLC, ANC and platelet counts (p>0.05) (Table 1).

On subgroup analyses; neonates with Gram negative sepsis (n=21) exhibited significantly higher levels of sE-selectin than infants with Gram positive sepsis (n=8), (p=0.04). Infected preterm infants (n=12) had similar sE-selectin levels when compared with infected term infants (n=17), (p=0.10). Regarding the onset of sepsis, we did not find any significant difference for sE-selectin levels when comparing early and late onset sepsis subgroups (p>0.05) (Table 3).

Infected preterm infants (n=12) had higher sE-selectin levels compared with non-infected (n=7) and control preterm infants

(n=6) (125.0 \pm 43.4 ng/ml vs 95.0 \pm 44.2 ng/ml; 72.9 \pm 26.9 ng/ml, p=0.001; p=0.04, respectively). Infected term infants (n=17) had higher sE-selectin levels compared with non-infected (n=9) and control term infants (n=9) (179.4 \pm 88.1 ng/ml vs 101.1 \pm 56.9 ng/ml; 81.1 \pm 33.7 ng/ml, p=0.012; p<0.001, respectively).

Evaluation of different laboratory tests as diagnostic markers for sepsis

Table 4. summarizes the sensitivity, specificity, predictive values and likelihood ratios of the five laboratory markers and combination of these markers, using the optimal cutoff values (CRP: 8 mg/l and sEselectin: 130 ng/ml, and I/T ratio ≥ 0.2). The ROC curves of sE-selectin, CRP, I/T ratio are shown in fig.1, comparison of each individual test using the optimal cutoff values showed that CRP has a higher sensitivity (86%) and specificity (97%) for detecting neonatal sepsis than all other laboratory markers. In contrast, sE-selectin had rather low sensitivity (59%) and moderate specificity (87%) for detecting infection.

Table (1): Clinical and laboratory characteristics of study population.

Characteristic	Infected (n=29)	Non- infected (n=16)	Control (n=15)	p value	
Birth weight (g)	2367 ± 828	2435 ± 846	2432 + 839	NS	
Gestational age (wks)	36.3 ± 3.7	36.6 ± 3.9	36.9 ± 2.6	NS	
Male sex	16 (55%)	8 (50%)	8 (53%)	NS	
Postnatal age (days)	8.7± 4.5	8.4± 3.6	8.8 ± 3.6	NS	
sE-selectin (ng/ml)	156.9 ± 77.0	88.8 ± 47.1#	86.7 ± 37.4	< 0.0001	
CRP (mg/l)*	48.0 (0-96)	0.5 (0-48)#	0 (0-8)	< 0.0001	
TLC	13.8 + 9.4	10.5 ± 5.1	9.9 ± 4.5	NS	
ANC	6.9 ± 4.2	5.2 ± 2.0	4.9 ± 1.9	NS	
I/T ratio	0.30 ± 0.17	0.12 ± 0.11#	0.12 ± 0.12	< 0.0001	
Platelet count	220 + 80	235 + 80	242 + 83	NS	

CRP: C-reactive protein; I/T ratio: immature to total neutrophil ratio; TLC: total leukocytic count; ANC: absolute neutrophil count; NS: not significant. Numbers of leukocytes, neutrophils and platelets are given in 1000/mm³.

All numbers are given as mean \pm SD or as median (range)* and as number (%).

p<0.0001 when compared with infected group, p>0.05 when compared with control group.

The combination of sE-selectin with either CRP or I/T ratio and the combination of I/T ratio and CRP slightly improved the specificity and positive predictive value, but significantly lowered the sensitivity and negative predictive value.

Prognostic value of sE-selectin

Higher plasma levels of sE-selectin were found in non-survivors vs. survivors (p=0.03) and in those with hemodynamic dysfunction (defined as inotropic and vasopressors requirement) compared with those without hemodynamic dysfunction (p=0.01) (Table 3)

Table (2): The causative organism in 29 infants with sepsis.

Gram positive sepsis	Number (%)	Gram negative sepsis	Number (%)
Staphylococcus aureus	3 (10.3%)	Klebseilla pneumonia	12 (41.3%)
Coagulase-negative	2 (6.9%)	Pseudomonas	4 (13.8%)
staphylococci		Aureogenosa	
Methicillin resistant	2 (6.9%)	Escherischia coli	3 (10.3%)
staphylococci	45.44		
Streptococcus fechlis		Serratia Marscens	1 (3.5%)
		Enterobacter spp	1 (3.5%)
Total	8 (27.6%)	Total	21 (72,4%)

Table (3): Soluble E-selectin levels in relation to gestational age, onset of sepsis, Gram stain of the organism, and prognosis.

	Soluble E-selectin (ng/ml)	p value
Infected preterm infants (n=12)	125,0 ± 43.4	NS
Infected full term infants (n=17)	179.4 ± 88.1	
Early onset sepsis (n=9)	156.6 ± 74.4	
Late onset sepsis (n=20)	170.0 ± 79.5	NS
Gram negative sepsis (n=21)	174.0 ± 81.4	
Gram positive sepsis (n=8)	111.9 ± 39.5	0.04
Hemodynamic dysfunction (n=11)	176.0 ± 79.7	
No hemodynamic dysfunction (n=18)	96.4 ± 41.7	0.01
Non-survivors (n=8)	188.0 ± 80.7	
Survivors (n=21)	110.5 + 61.7	0.03

NS: not significant.

Table (4): Sensitivity, specificity, predictive values and likelihood ratios of laboratory markers in early diagnosis of neonatal sepsis.

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	LR-
CRP	8 mg/L	86	97	96	88	28.7	0.11
I/T ratio	>0.20	76	87	85	79	5.8	0.28
sE-selectin	130 ng/ml	59	87	81	69	4.5	0.32
TLC	< 5000 or >20000/mm ³	48	77	67	62	2.1	0.68
ANC	<2000 or >75000/mm ³	55	74	67	64	2.1	0.61
Platelet count	<150000/mm ³	41	87	50	52	1.1	0.99
CRP + sE-selectin		45	100	100	65	∞	0.55
I/T ratio + CRP		62	100	100	74	- 00	0.38
I/T ratio+ sE-selectin		55	94	89	69	9.2	0.48

CRP: C-reactive protein; I/T ratio: immature to total neutrophil ratio; TLC: total leukocytic count; ANC: absolute neutrophil count; PPV: positive predictive value, NPV: negative predictive value; LR+: positive likelihood ratio, LR-: negative likelihood ratio.

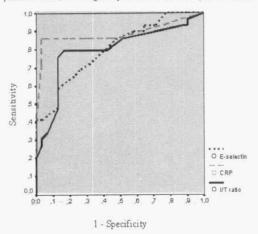


Figure 1. Receiver operating characteristic (ROC) curves comparing sE-selectin, CRP and I/T ratio for prediction of neonatal sepsis. The areas under the curve were: CRP: 0.89 (0.79-0.99); I/T ratio: 0.80 (0.68-0.92); and sE-selectin: 0.80 (0.69-0.91).

DISCUSSION

Early diagnosis of neonatal sepsis is difficult, because the clinical signs are neither uniform nor specific. However, empirical treatment should not be delayed because of the high mortality. The inability to adequately exclude the diagnosis of neonatal sepsis, on the other hand, can result in unnecessary and prolonged exposure to

antibiotics. Laboratory tests used to support diagnosis have shown variable predictive values.

The data presented here demonstrate several important findings related to altered functional status following neonatal sepsis. Infected newborn infants had higher plasma sE-selectin levels compared with noninfected and control infants. This confirms previous reports indicating elevated sEselectin in infected adults 19-21 and neonates. 10,22,23 Unlike the findings of Austgulen et al,22 we have found that levels of sE-selectin in infected preterm infants were not statistically different from those in infected term infants and that plasma sEselectin levels were higher in infected preterm infants compared with non-infected and control preterm infants. The divergent results may be due to differences in the criteria that were used to classify newborn infants as infected and the postnatal age of neonates at sampling. Other investigators reported increased levels of sE-selectin in premature infants with sepsis10 and with persistent inflammation of chronic lung disease.²⁷ These findings, indicate that the shedding of sE-selectin molecules is a

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component of the immune system and infection-induced immune response that is developed early in gestation.

In our population, sE-selectin levels were higher in patients with Gram negative sepsis, suggesting that the endothelium could be more intensely activated in these patients. The mechanisms by which the concentrations of soluble adhesion molecules increase in the plasma during inflammation are unclear but they probably involve the proteolytic cleavage of transmembrane proteins. 18 It is possible that increased amounts of sE-selectin in blood result from endothelial injury rather than mere activation, however, numerous studies have demonstrated that E-selectin is shed from cultured endothelial cells which are activated but have no evidence of injury or detachment. 19,28

The actual role these shed molecules play in the inflammatory process is far from clear. Initial cellular expression mediates the sequential process of placing effector inflammatory cells such as neutrophils in the region of the inflammatory stimulus. There is evidence that sE-selectin, as well as other adhesion molecules remain active once they are shed and can influence subsequent adhesion in several ways. Eselectin upregulates neutrophil CD11b, the ligand for ICAM-1 enhancing firm leukocyte attachment and transendothelial migration.²⁹ Since recombinant E-selectin can inhibit leukocyte adhesion to endothelium in vitro, it is likely that circulating E-selectin limits E-selectin mediated rolling of activated leukocytes via competitive binding of cell bound ligands, thus "downregulating" the inflammatory response.30

Diagnostic value for sE-selectin
In our study, the cut-off value for sE-selectin in diagnosis of neonatal sepsis was found to be 130 ng/ml. This value is lower than that reported in previous studies. A

cutoff value for sE-selectin for detection of sepsis in term neonates was 150 ng/ml demonstrated a sensitivity of 79% and a specificity of 61%. ²² Whereas, the cutoff value for sE-selectin was reported to be 174 ng/ml in detection of late onset sepsis in VLBW infants giving a sensitivity of 64% and specificity of 89% in the first 24 hours of suspected clinical sepsis. ¹⁰

Considering the high mortality and potential morbidity associated with neonatal sepsis, diagnostic tests with high sensitivity and negative predictive value are most desirable because all septic infants have to be identified. The lack of reliable clinical signs and laboratory tests often results in anticipatory antimicrobial treatment. In order to minimize the unnecessary use of antibiotics in false positive cases, tests need to have a reasonably high specificity and good positive predictive value. We found that sE-selectin has a low diagnostic sensitivity and specificity. Measuring CRP had the best sensitivity (86%) and specificity (97%) for the diagnosis of infection. The combination of sE-selectin with either CRP or I/T ratio slightly improved the specificity but adversely affected the sensitivity of these tests, so it can not be used as a diagnostic marker of neonatal sepsis. Furthermore, the likelihood ratio and ROC analysis demonstrated the higher diagnostic value of CRP and I/T ratio compared with sE-selectin as markers for

CRP has been thoroughly studied as a diagnostic tool in neonatal sepsis and also as an indicator of response to therapy⁴⁻⁸ The sensitivity of CRP in initial determinations for the detection of early-onset neonatal infection has been reported to vary from 35% to 65%, increasing to 94-97% by the time of third determination. CRP specificity varied in initial determination from 92% to 96% and decreased to 76-86% for the third measurement.³¹

Our findings are based on a single admission measurement, and we acknowledge that sequential testing might improve the diagnostic value of one, or all, of these parameters. Serial CRP have been shown to be more useful than a single measured CRP in the diagnostic evaluation of neonates with suspected infection. 32,33

Our data support the view of some authors that the leukocyte count has little value in differentiating infected from non-infected neonates ^{12,34} Although the specificity of the I/T ratio has been questioned;³⁵ in our study we determined a particular lack of sensitivity, as well as poor positive predictive value of I/T ratio and TLC in identifying the small number of initially asymptomatic at risk newborns who progressed to clinical sepsis, similar to the results reported recently by Ottolini et al.³⁶

Relation to the severity of sepsis
We have found that plasma sE-selectin
levels were higher in non-survivors and
those with hemodynamic dysfunction. A
striking positive relationship between sEselectin level and concomitant
hemodynamic dysfunction and multiple
organ failure was reported in adults with
sepsis. 19-21

Since the intensity of E-selectin expression and shedding appears to correlate with organ hypoperfusion and dysfunction, inactivation of cell-bound E-selectin might be expected to ameliorate these sequelae. Pretreatment of *Pseudomonas*-infused swine with a dual anti-E and anti-L-selectin monoclonal antibody significantly attenuated lung injury.37 In contrast, in a similar study in which the same antibody directed against E-selectin and L-selectin was administered to adult baboons before infusing a lethal dose of Escherichia coli, no protection from neutrophil accumulation in organs and no improvement in lung function occurred; furthermore, the animals treated with antibodies had more profound effects of pH and urine output and had decreased survival time. 38 In a preliminary study, administration of a murine monoclonal antibody to E-selectin to patients with septic shock was well tolerated and associated with dose-related improvement in oxygenation and trends for faster resolution of organ failure. 39

CONCLUSION

Plasma sE-selectin levels are elevated in neonatal sepsis. Higher levels were found in those with Gram negative sepsis than those with Gram positive sepsis. Gestational age and the onset of sepsis did not influence the levels of sE-selectin. sE-selectin had poor diagnostic value for prediction of neonatal sepsis compared with CRP and I/T ratio. However, high sE-selectin levels are associated with hemodynamic dysfunction and mortality and can be used as a prognostic indicator.

REFERENCES

- 1. Sinha A, Yokoe D, Platt R (2003). Epidemiology of neonatal infections: experience during and after hospitalization. Pediatr Infect Dis J; 22: 244-51.
 2. Gredes JS (1991). Clinicopathologic approach to the diagnosis of neonatal sepsis. Clin Perinatol; 18: 361-81.
- 3.Rodwell RL, Leslie AL, Tudehope DI (1988). Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr; 112: 761-7.
- **4.Krediet T, Gerards L, Fleer A, vanStekelenburg G (1992).** The predictive value of C-reactive protein and I/T-ratio in neonatal infection. J Perinat Med; 20: 479-85.
- 5.Berger C, Uhelinger J, Ghelfi D, Blau N, Fanconi S (1995). Comparison of Creactive protein and white blood cell count

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with differential in neonates at risk for septicemia. Eur J Pediatr; 154: 138-44. 6.Manucha V, Rusia U, Sikka M, Faridi MM, Madan N (2002). Utility of hematological parameters and C-reactive protein in the detection of neonatal sepsis. J Pediatr Child Health; 38: 459-64. 7.Seibert K, Yu VYH, Doery JCG (1990). The value of C-reactive protein measurement in the diagnosis of neonatal infection. J Pediatr Child Health; 26: 267-70.

8. Hatherill M, Tibby SM, Sykes K, Turner C, Murdoch IA (1999). Diagnostic markers of infection: comparison of procalcitonin with C reactive protein and leukocyte count. Arch Dis Child; 81: 417-21.

9.Ozdemir A, Oygur N, Gultekin M, Coskun M, Yegin O (1994). Neonatal tumor necrosis factor, interleukin-1 alpha, interleukin-1 beta and interleukin-6 response to infection. Am J Perinatol; 11: 282-5.

10.Ng PC, Cheng SH, Chui KM, Fok TF, Wong MY, Wong W, Wong RPO, Cheung KL (1997). Diagnosis of late onset neonatal sepsis with cytokines, adhesion molecule, and C-reactive protein in preterm very low birth weight infants. Arch Dis Child Fetal Neonatal Ed; 77: F221-F227.

11.Berner R, Tuksen B, Clad A, Forster J, Brandis M (2000). Elevated gene expression of interleukin-8 in cord blood as a sensitive marker for neonatal infection. Eur J Pediatr; 159: 205-10.

12. Reyes CS, Garcia-Munoz F, Reyes D, Gonzalez G, Dominguez C, Domenech E (2003). Role of cytokines (interleukin-1 beta, 6, 8, tumor necrosis factor-alpha, and soluble receptor of interleukin-2) and C-reactive protein in the diagnosis of neonatal sepsis. Acta Pediatr; 92: 221-7.

13.Blommendahl J, Janas M, Laine S, Miettinen A, Ashorn P (2002). Comparison of procalcitonin with CRP and differential

white blood cell count for diagnosis of culture-proven neonatal sepsis. Scand J Infect Dis; 34: 620-2.

14.Ng PC, Li K, Wong RPO, Chui KM, Wong E, Fok TF (2002). Neutrophil CD64 Expression: A sensitive diagnostic marker for late-onset nosocomial infection in very low birthweight infants. Pediatr Res; 51: 290-303.

15.Bevilacqua MP, Stengelin S, Gimbrone MA, Seed B (1989). Endothelial leukocyte adhesion molecule-1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. Science; 243:1160-5.

16.Springer TA (1990). Adhesion receptors of the immune system. Nature; 346: 425-34

17. Endo S, Inada K, Yamada Y, Takakuwa T, Nakae H, Kasai T, Koike S, Inoue Y, Niimi M, Wakabayashi G, Taniguchi S (1996). Levels of soluble adhesion molecules and cytokines in patients with septic multiple organ failure. J Inflam; 46: 212-9.

18.Gearing AJH, Newman W (1993). Circulating adhesion molecules in disease. Immun Today; 14: 506-12.

19.Newman W, Beall DB, Carson CW, Hunder GG, Graben N, Randhawa ZI, Gopal TV, Weiner-Kronish J, Matthay MA (1993). Soluble E-selectin is found in supernatants of activated endothelial cells and is elevated in the serum of patients with septic shock. J Immun; 150: 633-54.

20.Cummings CJ, Sessler CN, Beall LD, Fisher BJ, Best AM, Fowler AA (1997). Soluble E-selectin levels in sepsis and critical illness: correlation with infection and hemodynamic dysfunction. Am J Respir Crit Care Med; 156: 431-7.

21.Reinhart K, Bayer O, Brunkhorst F, Meisner M (2002). Markers of endothelial damage in organ dysfunction and sepsis. Crit Care Med; 30 (5 Suppl): S302-12.

22. Austgulen R, Arntzen KJ, Haereid PE, Aag S, Dollner H (1997). Infections in neonates delivered at term are associated with increased serum levels of ICAM-1 and E-selectin. Acta Pediatr; 86: 274-80.

23. Dollner H, Vatten L, Austgulen R (2001). Early diagnostic markers for neonatal sepsis: Comparing C-reactive protein, interleukin-6, soluble tumor necrosis factor receptors and soluble adhesion molecules. J Clin Epidemiol: 54:11251-7.

24.Tollner U (1982). Early diagnosis of septicemia in the newborn: clinical studies and sepsis score. Eur J Pediatr; 138: 331-7.

25.Da Silva O, Hammerberg O (1994). Diagnostic value of leukocyte indices in late neonatal sepsis. Pediatr Infect Dis J; 13: 409-10.

26. Peakman M, Senaldi G, Liossis G, Gamsu HR, Vergani D (1992). Complement activation in neonatal infection. Arch Dis Child; 67: 802-7. 27. Ramsay PL, Smith EO, Hegemier S, Welty S (1998). Early clinical markers for the development of bronchopulmonary dysplasia: Soluble E-selectin and ICAM-1. Pediatr; 102: 927-32.

28. Pigott R, Dillon LP, Hemingway 1H, Gearing AJ (1992). Soluble forms of Eselectin, ICAM-1 and VCAM-1 are present in the supernatants of cytokine activated cultured endothelial cells. Biochem Biophys Res Commun; 187: 584-9.

29.Lo SK, Lee S, Ramos RA, Lobb R, Rosa M, Chi-Rossa G, Wright SD (1991). Endothelial-leukocyte adhesion molecule 1 stimulates the adhesive activity of neutrophil integrin CR3 (CD11a/CD18, Mac-1, alpha m beta 2) on human neutrophils. J Exp Med; 173: 1493–1500. 30.Lobb R, Chi-Rosso G, Leone DR, Rosa MD, Bixler S, Newman BM, Lyhowskyj S, Benjamin CD, Gougas IG, Goelz SE (1991). Expression and functional characterization of a soluble form of endothelial-leukocyte adhesion molecule.

J Immunol; 124: 129-47.

31. Fowlie PW, Schmidt B (1998). Diagnostic tests for bacterial infection from birth to 90 days—a systematic review. Arch Dis Child Fetal Neonatal Ed; 78: F92–F98. 32. Pourcyrous M, Bada HS, Korones SB, Baseliski V, Wong SP (1993). Significance of serial C-reactive protein responses in neonatal infection and other disorders. Pediatr; 92: 431-5.

33. Nuntnarumit P, Pinkaew O, Kitiwanwanich S (2002). Predictive values of serial C-reactive protein in neonatal sepsis. J Med Assoc Thai; 85 Suppl; 4:S1151-8.

34.Kite P, Millar MR, Gornham P (1988). Comparison of 5 tests in diagnosis of neonatal bacteremia. Arch Dis Child; 63: 639-43.

35. Schelonka RL, Yoder BA, des Jardins SE, Hall RB, Buttler J (1994). Peripheral leukocyte count and leukocyte indices in healthy newborn term infants. J Pediatr; 125: 603-6.

36.Ottolini MC, Lundgren K, Mirkinson LJ, Cason S, Ottolini MG (2003). Utility of complete blood count and blood culture screening to diagnose neonatal sepsis in the asymptomatic at risk newborn. Pediatr Infect Dis J; 22: 430-4.

37. Ridings PC, Windsor ACJ, Jutila MA, Blocher CR, Fisher BJ, Sholley MM, Sugerman HJ, Fowler AA (1995). A dual-binding antibody to E- and L-selectin attenuates sepsis-induced lung injury. Am J Respir Crit Care Med; 152: 247–53.

38. Carraway MS, Welty-Wolf KE, Kantrow SP, Huang YC, Simonson SG, Que LG, Kishimoto TK, Piantadosi CA (1998). Antibody to E- and L-selectin does not prevent lung injury or mortality in septic baboons. Am J Resp Crit Care Med; 157: 938-49.

39. Friedman G, Jankowski S, Shahla M, Goldman M, Rose RM, Kahn RJ, Vincent J (1996). Administration of an antibody to E-selectin in patients with septic shock. Crit Care Med; 24:229-33.

تقييم ال "إى - سيليكتين" القابل للذوبان كدلالة للعدوى في الأطفال حديثي الولادة هشام عبد الهادي، ميساء زكي

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الملخص العربي

الهدف من البحث:

تقييم ال "إى - سيليكتين" القابل للذوبان كدلالة للعدوى في الأطفال حديثي الولادة مقارنة بالتحاليل المعروفة لتشخيص هذا المرض مثل السي أربى"، عدد كريات الدم البيضاء، عدد خلايا التيوتروفيل" المطلق، نسبة خلايا "النيوتروفيل" الغير ناضعة إلى نسبة خلايا "النيتروفيل" الكلية وكذا تقييم قيمته التكهنية.

تصميم وطريقة البحث:

شمل البحث ٤٥ طفل حديث الولادة يشتبه بإصابتهم بالعدوى. وقد أثبتت مزارع الدم إصابة ٢٩ منهم بالعدوى بينما ثبت عدم إصابة ١٦ منهم بالعدوى بينما شملت مجموعة المقارنة ١٥ طفل سليم حديث الولادة لا يعانوا من أى أعراض للعدوى، وقد تم عمل فحص إكلينيكي شامل لهؤلاء الأطفال وتم قياس مستويات ال "إى سيليكتين" القابل للذوبان في البلازما وكذا مستويات ال"سي أر بي"، عدد كريات الدم البيضاء، عدد خلايا النيوتروفيل" الكلية.

نتائج البحث:

في الأطفال المصابين بالعدوى كانت مستويات ال "إى - سيليكتين" القابل للذوبان في البلازما أعلى من مثيلاتها في الأطفال الغير مصابين بالعدوى و في الأطفال في مجموعة المقارنة، كما كانت مستويات ال"إى - سيليكتين" القابل للذوبان في بلازما الأطفال المصابين بالبكتريا سلبية الجرام أعلى من مثيلاتها في الأطفال المصابين بالبكتريا البجابية الجرام، ولم يكن هناك تأثير يذكر للعمر الرحمي أو لميعاد حدوث العدوى على مستويات ال "إى-سيليكتين" القابل للذوبان في بلازما الأطفال المصابين بالعدوى. وقد وجدنا أن القيمة الفاصلة للتبوء بالعدوى لل"إى - سيليكتين" القابل للذوبان في البلازما هي ١٣٠ نانوجرام/مللي، وكانت لل "سي أر بي" أعلى قيمة تشخيصية بينما كانت القيمة التشخيصية لل "إى - سيليكتين" ضعيفة في تشخيص العدوى في الأطفال حديثي الولادة، كما أننا قد وجدنا أن مستويات ال "إى - سيليكتين" القابل للذوبان في بلازما الأطفال الذين توفوا أعلى منها في الأطفال الذين لم يتوفوا وكذا كانت أعلى في الأطفال الذين عانوا من اضطراب في الدورة الدموية.

الخلاصة:

ارتفعت مستويات ال"إى - سيليكتين" القابل للذوبان في البلازما في الأطفال المصابين بالعدوى، و كانت مستوياته في بلازما الأطفال المصابين بالبكتريا إيجابية في بلازما الأطفال المصابين بالبكتريا إيجابية الجرام أعلى من مستوياته في الأطفال المصابين بالبكتريا إيجابية الجرام، ولم يكن هنالك تأثير يذكر للعمر الرحمي أو لميعاد حدوث العدوى على مستويات ال"إى - سيليكتين" القابل للذوبان في بلازما الأطفال المصابين بالعدوى. كانت القيمة التشخيصية لل"إى - سيليكتين" ضعيفة في تشخيص العدوى في الأطفال حديثي الولادة ولكن وجد له قيمة تكهنية عالية حيث كانت مستوياته في بلازما الأطفال الذين توفوا أعلى منها في الأطفال الذين لم يتوفوا وكذا كانت أعلى في الأطفال الذين عانوا من اضطراب الدورة الدموية.

