Soluble Intercellular Adhesion Molecule-1 (sICAM-1) For Early Diagnosis of Neonatal Infections

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We investigated the validity of circulating soluble intercellular adhesion molecule-1 (sICAM-1) as an early immunological marker of neonatal sepsis as compared to C-reactive protein (CRP), immature to total neutrophils ratio (I/T) and blood culture assays. The study included 28 full term neonates with clinical manifestations of sepsis, 10 of them had suspected sepsis “Group I” with negative blood culture, positive CRP during 1st week of life and one or more risk factors for infections. The other 18 neonates had proven sepsis “Group II”; with positive blood culture and positive CRP. 14 normal age and sex matched controls “Group III” were also included. Serum sICAM-1 concentrations (ng/ml) were measured using enzyme linked immunosorbent assay (ELISA) in two successive blood samples; before (S1) and one week after (S2) the start of antibiotics respectively. The mean value of I/T ratio was significantly higher in both S1 and S2 (P<0.05; P<0.001 respectively) in septic neonates compared with controls. In addition, a significant difference (P<0.05) was detected in S2 between mean CRP levels in group I (9.6±15.7 mg/dl) and group II (17.3±30.0 mg/dl). The mean values of sICAM-1 in (S1) of septic groups I and II (445.7±138.5 and 512.8±240.9 ng/ml respectively) were significantly higher (P<0.05) than those of control group (364.0±67.4). In contrast, in (S2) insignificant differences were detected between both groups (392.6±149.8 and 420.0±184.7 respectively) and controls. A positive correlation was revealed between CRP and sICAM-1 values in (S1) (r=0.3, P<0.05). Positive correlations were also detected between sICAM-1 levels and leukocytic counts (r=0.3, P<0.05) and CRP (r=0.5, P<0.001) in (S2) while, negative correlation was detected between sICAM-1 levels and platelet counts (r= -0.5, P<0.001). In conclusion, serum concentration of ICAM-1 is a potential marker for diagnosis of neonatal sepsis at its early stages.

Neonatal sepsis is a major cause of morbidity and mortality in the newborn despite of improvement in the antimicrobial therapy. In Egypt neonatal septicemia is considered the most serious problem and represents about 60% of neonatal deaths in Neonatal Intensive Care Units; (NICU). In the NICU of Tanta University hospital the incidence of neonatal sepsis was 26.3% (Shebl, 2003). In 1999, the World Health Organization (WHO) reported that infectious diseases are associated with 30-40% of neonatal deaths.

Administration of antibiotics renders many neonates susceptible to side effects of antimicrobial agents, increases hospital costs, and promotes the development and spread of resistant bacterial strains. Because of the danger of delayed diagnosis, clinicians must pay careful attention to the perinatal risk factors of sepsis in a newborn infant in order to start antibiotic therapy even in infants who are asymptomatic but at high risk (Liberman et al., 2000; Afroza, 2006). Early onset sepsis presents in the first 5-7 days of life. It is usually multi-system fulminant illness with prominent respiratory systems. Typically, the infant has acquired organism during the intra-partum period. Acquisition of other organisms is associated with birth process. The late onset disease is more common after the first week of life. Those babies usually have an identifiable focus, most often meningitis in addition to sepsis (Chiesa et al., 2004).

Nosocomial sepsis occurs in high risk newborn infants. Its pathogenesis is related to the underlying illness and debilitation of the infants, the flora in NICU environment, and invasive monitoring techniques (Jumah & Hassan, 2007). Early diagnosis of sepsis in the
neonates is often difficult as symptoms and signs are usually non-specific and are associated with characteristics of the causative organism and the body response to invasion. In addition, no single laboratory test has been found to have acceptable specificity and sensitivity for predicting infection. Isolation of bacteria from blood is the standard and most-specific method to diagnose neonatal sepsis. Studies have reported that, in most circumstances, if blood culture results are not reported as positive by 48 hours, then empiric institution of antibiotics may be discontinued (Gonzalez et al., 2003).

Many diagnostic tests such as total leukocytic count, immature to total Neutrophil ratio; I/T and CRP or groups of tests are utilized to diagnose or confirm sepsis (Radetsky, 1995). Therefore parameters that could be useful in the early diagnosis of infections are urgent and are needed to identify truly infected neonates (Nupponen et al., 2001). Certain immunological markers have been evaluated as early indicators of neonatal sepsis that can improve the diagnostic sensitivity and useful for early termination of antimicrobial treatment. Chemokines, cytokines (IL-6, IL-8) and component of the immune pathway were studied extensively in preterm and term newborns (Schultz et al., 2002). However, these markers are not sensitive enough for early diagnosis of neonatal sepsis (Ng, 2004). Leukocytes-endothelial adhesion has been identified as an early step in cellular extravasation and development of an inflammatory response to bacterial infections. These events are mediated by a number of adhesion molecules including intercellular adhesion molecule-1 (ICAM-1) (Dustin et al., 1986). ICAM-1 is a member of immunoglobulin superfamily, and it is responsible for stable adhesion of leukocytes to endothelium, a step which precedes leukocyte emigration to sites of tissue injury. Several studies have investigated serum level status of adhesion molecules and their relation to: normal immune function, postnatal, sex and mode of delivery (Phocas et al., 1998).

The aim of the present study was to determine whether serum concentration of ICAM-1 can be used as a possible marker for diagnosis of neonatal sepsis at its early stages.

**Materials and Methods**

**Subjects**

A total of 42 neonates, were enrolled in this study. They were admitted to Al-Shohadaa centre. All neonates were full-term, their ages ranged from 1 to 6 days, their body weight at the time of admission ranged from 1.9 kg to 3.5 kg. 28 of neonates were admitted to NICU with symptoms and signs suggestive of clinical sepsis that occurred during the first week of life. The remaining 14 neonates were age, sex and weight matched normal healthy controls. All neonates were subjected to: (I) Clinical history including the antenatal history of maternal fever, maternal drugs intake and the occurrence of infections especially in the first trimester, the natal history to detect a risk factor for neonatal infections as premature rupture of membranes >18hrs., maternal fever 38°C, vaginal bleeding or presence of foreign body as endotracheal or chest tubes and mode of delivery “vaginal, caesarean section or complicated trauma. The postnatal history of “Apgar score”, pallor, jaundice and convulsion was also recorded. (II) Clinical examination including (a) General examination (Weight, length, Skull circumference, vital signs (pulse, temperature, blood pressure, respiratory tract disorders), neonatal reflexes (moror’s, grasping and sucking reflex), (b) Examination for detection of clinical signs of sepsis: General signs, Neurological, Respiratory; Cardiovascular, Gastrointestinal dysfunction (III) Laboratory investigations: Total and differential leukocytic counts, R.B.Cs and Platelet counts, Hb%, immature to total neutrophil ratio (I/T), and determination of serum CRP levels.

Two ml of venous blood were obtained from each patient and control, one ml was dispensed into a tube containing (EDTA) for complete blood picture, and one ml was left to clot and serum was separated and stored at –20°C until used for sICAM-1 detection. Two blood samples were obtained from each neonate: one at admission (S1) before the start of antibiotic treatment for laboratory investigations including blood culture and sICAM-1 detection. Another sample (S2) was obtained after one week of admission and after the start
of antibiotic treatment, for laboratory investigations and sICAM-1 detection.

Methods

- For determination of immature to total neutrophil ratio (I/T), a smear was made from EDTA anti-coagulated blood sample and stained with May-Grünwald Giemsa. All immature neutrophil forms (segmented and band forms) were counted and the I/T ratio was calculated. Ratio ≥ 0.2 indicates sepsis (Keijzer & Willems, 2006).

- Determination of serum CRP levels was carried out using latex serology detection kit (Pepy, 1981).

- Blood culture was carried out on the first day of admission before starting antibiotic treatment (Sumaya & Jenson, 1992).

- Determination of sICAM-1 concentration in serum using quantitative sandwich enzyme linked immunosorbent assay (ELISA) kit (R&D system, USA). A monoclonal antibody specific for sICAM-1 has been pre-coated onto a 96 well micro-plate. Standards, samples, controls and conjugate are pipetted in the wells. The intensity of the colour is proportion to the amount of sICAM-1 bound. The absorbance (OD) was measured at 450 nm using an ELISA reader. A standard curve was constructed from the standards and sICAM-1 concentrations (ng/ml) in the samples were determined from the standard curve.

Statistical Analysis

Data were computed using the statistical software package SPSS, version 9.05 (SPSS inc., Chicago, Illinois): quantitative data inform of mean ±SD and range and for qualitative data in form of number and percentage, Student t-test for two independent variables and Paired t-test for paired variables, and Pearson correction coefficient (r).

Results

The current study included 42 neonates, 28 of them had clinical manifestations and laboratory findings of sepsis and 14 were normal controls.

According to the results of blood culture and laboratory investigations neonates with sepsis were divided into 2 groups:

Group I “Suspected Sepsis” comprised 10 neonates with possible or suspected sepsis i.e. >2 of clinical signs of sepsis, all had abnormal leukocyte counts, positive CRP, I/T ratio ≥ 0.2 and initially negative blood cultures. They also had one or more of the risk factors for infections such as “premature rupture of membranes >18 hours, choriomnionitis, intrapartum maternal fever >38°C, maternal history of urinary tract infection and complicated traumatic delivery. They were 6 females and 4 males, their mean age was (1.40±0.98) days and mean body weight was (2.80± 0.62) kg.

Group II “Proven Sepsis” comprised 18 neonates with proven sepsis; all had ≥2 of clinical signs of sepsis, abnormal leukocytic counts, positive CRP, I/T ratio ≥0.2 and positive blood cultures. They were 8 females and 10 males, their mean age was (1.40±1.03) days and mean body weight was (3.00± 0.60) kg.

Group III “Controls” included 14 age and sex matched normal healthy neonates; with no clinical manifestations or laboratory findings denoting neonatal infections. They were 9 females and 5 males. Their mean age was (1.42±1.12) days and mean body weight was (2.88±0.46) kg (Table 1).
Table 1. Demographic data of neonates with sepsis and controls

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
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<tbody>
<tr>
<td></td>
<td>“Suspected sepsis” (10)</td>
<td>“Proven sepsis” (18)</td>
<td>“Normal Controls” (14)</td>
</tr>
<tr>
<td>Age “days” (Mean ±SD)</td>
<td>1.40 ± 0.98</td>
<td>1.40 ± 1.03</td>
<td>1.42 ± 1.12</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>4/6</td>
<td>10/8</td>
<td>5/9</td>
</tr>
<tr>
<td>Body weight “kg” (Mean ±SD)</td>
<td>2.80 ± 0.62</td>
<td>3.00 ± 0.60</td>
<td>2.88 ± 0.46</td>
</tr>
<tr>
<td>*CRP</td>
<td>+ve</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>I/T ratio</td>
<td>&gt;0.2</td>
<td>&gt;0.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Blood culture</td>
<td>-ve</td>
<td>+ve</td>
<td>-ve</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>&gt; one symptoms from at least 3 categories</td>
<td>&gt; one symptoms from at least 3 categories</td>
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CRP: C-reactive protein; *+ve means > above zero (William et al,1998); I/T: Immature to total neutrophil ratio; VD = vaginal delivery; CS = Caesarean section

Results of Laboratory Findings of the First Sample (S1) [before the start of Antibiotic Treatment] and the Second Sample (S2) [after the start of Antibiotic Treatment]

In group I “suspected sepsis” the mean values of Hb (gm/dL), leukocytic count (x10^3/mm^3), platelets count (x10^3/mm^3), I/T ratio and CRP (mg/dL) in (S1) were (14.6±3.2), (16.1±12.3), (198.3±46.9), (0.09±0.07) and (28.8±27.8) respectively. While, in group II “proven sepsis” they were (13.1±3.49), (13.8±9.9), (195.8±81.8), (0.17±0.09) and (38.00±19.40) respectively. Only the I/T ratio and CRP values showed significant increase (P<0.05) in neonates with sepsis (group I & II) than those of controls (0.06±0.04) and zero respectively, while other parameters showed insignificant differences (P>0.05), (Table 2).

In the second sample (S2); a week after antibiotic therapy the mean values of I/T ratio and CRP of (group I & II) were significantly higher than those of controls (P1<0.001) & (P2<0.05) respectively, (Table 2). Comparison of I/T values between S1 & S2 revealed no significant difference (P2>0.05) in group I and a highly significant difference (P3<0.001) in group II, (fig. 1).

The results also revealed significant decreases in the mean value of CRP of (S2) in both groups as compared with (S1) (P3<0.05) (Table 2).

Results of Blood Culture

The microorganisms that were isolated from blood cultures of group II were Klebsiella pneumoniae (55.6%), Pseudomonas aeruginosae (38.9%) and Staphylococcus aureus (5.5%) (data are not shown).
Table 2. Hematological and Serological results in neonates with sepsis and controls

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=10)</th>
<th>Group II (n=18)</th>
<th>Group III (n=14)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1</td>
<td>S2</td>
<td>S1</td>
<td>S2</td>
</tr>
<tr>
<td>Hb. &quot;gm/dL&quot;</td>
<td>14.6±3.2</td>
<td>13.2±2.07</td>
<td>13.1±3.49</td>
<td>13.3±21.7</td>
</tr>
<tr>
<td>Leucocytes (10^3/mm^3)</td>
<td>16.1±12.3</td>
<td>12.03±4.6</td>
<td>13.8±9.9</td>
<td>13.5±5.8</td>
</tr>
<tr>
<td>I/T ratio</td>
<td>0.09±0.07</td>
<td>0.1±0.05</td>
<td>0.17±0.09</td>
<td>0.08±0.03</td>
</tr>
<tr>
<td>Platelets (10^3/mm^3)</td>
<td>198.3±46.9</td>
<td>180.3±77.6</td>
<td>195.8±81.8</td>
<td>210±117.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>28.8±27.8</td>
<td>9.6±15.7</td>
<td>38±19.4</td>
<td>17.3±30</td>
</tr>
</tbody>
</table>

I/T ratio: immature to total neutrophils ratio, CRP = C-reactive protein, Hb = Haemoglobin, p=between patient groups & controls in S1, \(P_1\)= between patient groups & controls in S2, \(P_2\)= between S1 & S2 in group I, \(P_3\)= between S1 & S2 in group II

Figure 1. I/T Ratio in the First and Second Samples of Neonates with Sepsis and Controls.
Measurement of sICAM-1 Concentrations by ELISA

The cut off value of sICAM-1 concentrations was calculated from the mean values of the control group + 2SD, this value was 400 ng/mL. Values higher than that of the cut off were considered positive. 60 % and 72% among group I and II neonates respectively had higher levels of sICAM-1 in the first sample as compared with controls. Significant differences ($P<0.05$) between groups were detected in (S1) while, no significant differences were observed in (S2) (40%, 50%) respectively.

The mean±SD values of sICAM-1 concentration in S1 were (445.7±138.5), (512.8±240.9) and (364±67.4) in group I, II and III respectively. Significant difference ($P<0.05$) was detected between groups.

In S2; the values were (392.6±149.8), (420±184.7) and (366.7±50.9) respectively (Table 3), with insignificant difference between groups. The difference between S1 and S2 values was significant in neonates with suspected sepsis ($P_2<0.001$) and proven sepsis ($P_3<0.05$), (Fig 2).

Table 3. sICAM-1 concentrations "ng/ml" in the first and second samples from neonates with sepsis and controls

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Suspected sepsis&quot; (n=10)</td>
<td>&quot;Proven sepsis&quot; (n=18)</td>
<td>&quot;Controls&quot; (n=14)</td>
</tr>
<tr>
<td>First sample (S1) [Mean ± SD]</td>
<td>445.7 ± 138.5</td>
<td>512.8 ± 240.9</td>
</tr>
<tr>
<td>Second Sample (S2) [Mean ± SD]</td>
<td>392.6 ± 149.8</td>
<td>420 ± 184.7</td>
</tr>
</tbody>
</table>

$P$=between groups in S1, $P_1$= between groups in S2, $P_2$= between S1 & S2 in group I, $P_3$= between S1 & S2 in group II

Figure 2 Serum Levels of sICAM-1 (ng/ml) in the first and Second Samples of Neonates with Sepsis and Control.
Correlation Studies

In S1, there was a significant positive correlation only between sICAM-1 level and CRP ($r=0.3$, $P<0.05$) (Fig. 3). While, in S2 a positive correlation was detected between sICAM-1 and both CRP level ($r=0.5$, $P<0.01$) (Fig. 4) and leukocytes count ($r=0.3$, $P<0.05$) (Fig. 5) and a negative correlation between sICAM-1 level and platelet count ($r=-0.5$, $P<0.001$) (Fig. 6).

**Figure 3.** Correlation between sICAM-1 and CRP Concentrations in the First Sample of Neonates with Sepsis

**Figure 4.** Correlation between sICAM-1 and CRP Concentrations in the Second Sample of Neonates with Sepsis

**Figure 5.** Correlation between sICAM-1 Concentrations and Leukocytic Counts in the Second Sample of Neonates with Sepsis.

**Figure 6.** Correlation between sICAM-1 Concentrations and Platelets Counts in the Second Sample of Neonates with Sepsis.
Discussion

Neonatal sepsis is a common and life-threatening disorder. Since, its outcome and prognosis depend on early and efficient antibiotic therapy; there is a need for a sensitive and specific marker for diagnosis of sepsis at the earliest stage of the disease (Eicher & Annibale, 2002). Current evidence suggests that promising markers may be useful for early termination of antimicrobial treatment. Some simple haematological investigations such as CBC, CRP, I/T ratio and blood culture were analyzed according to the haematological scoring system (HSS). Their sensitivity and specificity, allow a more systemic approach to decisions regarding antibiotic therapy (El-Kerdani et al., 2001), but none of the current diagnostic tests are sensitive enough to influence the clinical decision for withholding antibiotic treatment of the onset of suspected infection (Ng, 2004). Isolation of bacteria from a central body fluid (usually blood) is the standard and most-specific method to diagnose neonatal sepsis. Bacteremia has been found to occur in 32.3% of infections, with mortality rates ranging from 15% to 50%. Studies have reported that, in most circumstances, if blood culture results are not reported as positive by 48 hours, then empiric institution of antibiotics may be discontinued (Bhandari et al., 2008). Certain immunological parameters such as assessment of the inflammatory mediators produced during immune response have been evaluated as early indicators of neonatal sepsis and may improve the diagnostic accuracy. ICAM-1 has a crucial role in the initial steps of leukocyte emigration into sites of infection. It is responsible for stable adhesion of leukocytes to endothelium, a step which precedes leukocyte emigration to sites of tissue injury (Vesikari, 1999).

The aim of the present study was to determine whether serum ICAM-1 level can be used as a possible marker for diagnosis of neonatal sepsis at its early stages, since the early clinical signs are often insidious and non-specific. Laboratory investigations such as the total and differential leukocytic counts, Hb%, immature to total neutrophil ratio (I/T), Platelet counts, determination of serum CRP and blood culture were evaluated and compared with serum concentrations of ICAM-1 measured by ELISA. Two blood samples were obtained from neonates with suspected sepsis; who had negative blood cultures (group I) and proven sepsis who had positive blood cultures (group II). The first sample was taken at admission (S1) before the start of antibiotic treatment and a second sample (S2) after one week of the start of antibiotic treatment.

As regards to the haematological findings among the studied groups, it was found that anaemia is not significant in neonates with sepsis when compared to control group (table 2). This finding agrees with that of Ericksson, (1983) but controversial with El-Kerdani et al. (2001) who found that anaemia is significant in neonates with proven sepsis and in those with early sepsis which may be due to the haemolytic process of septicaemia. The mean value of the total leukocytic count (TLC) in this study was statistically insignificant when compared with that of the control group in both (S1) and (S2) samples. This result agrees with the study done by El-Kerdani et al. (2001) who found variation of leukocytic count in the form of either leukocytosis or leukopenia which may be due to bone marrow depression, depletion of storage pool (destruction of neutrophils) and redistribution of circulating neutrophils to migrating one (pseudo-neutropenia). However, Boyle et al. (1990) stated that TLC is the least useful index for sepsis

In the present study, I/T ratio in the first and second samples was found to be highly
significant in neonates with sepsis when compared with control group. This finding agrees with that of El-Kerdani et al. (2001) and supports the opinion that an I/T ratio higher than 0.2 is associated with increased risk of bacterial infection since more immature forms are seen in the peripheral blood, commonly known as band forms. However, Linda et al. (2006) and Frank, (2009) reported that elevation of I/T ratio may be observed with other pathological events. Therefore, when diagnosing sepsis, the elevated I/T ratio should be used in combination with other signs.

In this study, the platelet counts in the first and second samples showed insignificant differences between neonates with sepsis compared with control group. This agrees with Stoll et al. (1996) who reported that the use of platelet count is of limited value in establishing the diagnosis of neonatal infection and normal count does not exclude neonatal sepsis. However, El-Kerdani et al. (2001) found thrombocytopenia among cases with proven and early sepsis when compared to controls. A decrease of platelet count may be due to bone marrow depression, peripheral destruction and consumption of platelets in DIC. Ahmed et al. (2005) showed that the mortality rate is higher when neonates have anemia, thrombocytopenia, leukopenia and neutropenia.

The CRP values of the first and second samples of septic neonates “group I and II” were found to be significantly higher than that of normal controls ($P<0.001$). These findings agree with Meisner (1996) who found that all septic neonates had positive CRP values and CRP might increase to its maximum and that increased values can remain elevated several days at pathological levels after the end of inflammation or after improvement of the clinical situation. It is interesting to note that there were significant differences in the mean values of CRP in the first and second samples between neonates with suspected and proven sepsis. These findings match with that of Peltolo & Jaakkola (1998) who reported that the CRP is a sensitive, early and reliable indicator of systemic inflammation. Although CRP is a preferred test, but it has many drawbacks: it is not always possible to differentiate bacterial from other types of inflammation as it reacts rather non specifically, its value does not rise significantly until 12-24 hours after the onset of infection, it might be normal in the early course of sepsis so it did not discriminate two infants with culture proven sepsis from non-infected control neonates at the time of admission. Previously, Kawamura & Nishida (1995) found that after birth CRP values are subjected to non specific changes which may reflect a physiological reaction to stress during labour. In additions De Bont et al. (1995) reported that CRP has a short half life (4-6 hours) and variable lag period between the clinical onset of the disease and elevated serum concentration. Thus, CRP seems to be less useful as a diagnostic test in the early stages of neonatal infections but, is more important in monitoring sepsis. Serial CRP measurements are also necessary for diagnosing sepsis (El-Kerdeni et al., 2001).

Several studies have investigated serum level status of adhesion molecules and their relation to: normal immune function, postnatal, sex and mode of delivery (Austgulen et al., 1997). However, participation of adhesion molecules in neonatal infections remains unclear and need more investigations.

In the current work, sICAM-1 was detected in serum samples of all neonates, suggesting its constitutive shedding. Phocas et al. (1998) documented that there is a constitutive shedding of soluble adhesion molecules e.g. E-selection and ICAM-1, since they are established components of the neonatal immune system from 24 weeks gestational age. Thus, it is likely to occur in neonatal
tissues from birth and not due to transport to foetal circulation during pregnancy.

In this study, sICAM-1 levels of the first sample were significantly ($P < 0.05$) increased in both neonates with suspected (group I) and proven sepsis “group II” when compared to controls “group III”. These findings agree with that of Dollner et al. (2001) who found highly significant increases in levels of sICAM-1 in infected neonates when compared with none infected. Kuster & Degitz (1993) previously reported that increased sICAM-1 might be a useful indicator for the early detection of neonatal sepsis, since it rises more frequently and significantly earlier than currently used indices. In contrast, Dollner et al. (2001) reported that measurement of sICAM-1 added no further diagnostic information to the assessment of CRP in possibly infected neonates. On the other hand, the present study revealed insignificant decreases in sICAM-1 in the second sample of both groups of neonate with sepsis which agrees with that of Austgulen et al. (1997) who found decreasing concentrations during the perinatal period, suggesting neonatal elimination.

In this study, 60% of neonates with suspected sepsis (group I) were found to have increased sICAM levels in the first sample compared to 70% of neonates with proven sepsis (group II). This finding may point out to the possible use of sICAM-1 in detection of neonates with suspected sepsis who have negative blood cultures. Kuster & Degitz (1993) reported that 23 of 28 babies with clinical sepsis but negative blood cultures had elevated sICAM-1and it remained low in 13 of 17 infants without clinical sepsis.

Austgulen et al. (1997) suggested that assessment of sICAM-1 levels may be used as a diagnostic tool with high sensitivity and moderate specificity only in term neonates with suspected infection. These findings are also supported by the results of Edgar et al. (1994) who studied the predictive value of soluble immunological mediators in neonatal infection such as tumour necrosis factor-α, interleukin-6, interleukin-8, ICAM-1 and CRP. They found that ICAM-1 measurement provided the most sensitive (88%) and specific (86%) single predictor of infection compared with sensitivity of positive blood culture (92%) and negative blood culture (82%). They stated also that combination of ICAM-1 with CRP increased the sensitivity for infection to 95% comprising 100% sensitivity for positive blood culture and 88% for negative blood culture and this will enable the identification of infants who will subsequently have a positive blood culture result within 3 hours of clinical deterioration. The negative predictive value of 97% suggested that this approach would also have a major role in confidently excluding infection as a cause of acute deterioration.

Correlation studies revealed significant positive correlations between sICAM-1 and CRP values in both first and second samples ($P < 0.05$) and ($P < 0.001$) respectively. This finding agrees with that of Edgar et al. (1994) who constructed a model to examine the independent effect of each measurement in predicting infection commencing with ICAM-1 as a single most sensitive indicator of infection. Moreover, this study revealed insignificant correlation between I/T ratio and sICAM-1 which also agrees with Engle et al. (1997) who stated that ratio of I/T neutrophils provides “some” diagnostic information but have limitations in sensitivity and specificity. In addition, Hansen et al. (2000) reported that sICAM-1 and CRP in combination are better than CRP as a primary test for identification of infection in babies < 5 days of age. Furthermore, Kuster & Degitz, (1993) concluded that increased sICAM-1 might be a useful indicator for the early detection of neonatal sepsis. Serum ICAM-1 rises more frequently and significantly earlier than
currently used indices. Another favourable feature of sICAM-1 is that only 20μL serum is needed for assay; this is an important advantage in new born babies.

It is concluded that sICAM-1 ELISA is a rapid, sensitive and more efficient test for early diagnosis of neonatal sepsis than CRP which is a late diagnostic test. Results can be obtained within hours, allowing treatment to start before having the conventional blood culture results which takes about 3 days. Additionally, early diagnosis of neonates with suspected sepsis can reduce the unnecessary use of antibiotic therapy and early discharge from hospital to avoid nosocomial infections. Moreover, the use of multiple markers, combining an early and late sensitive test will enhance the diagnostic accuracy of infected cases.

References


