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Research Article
Intercellular Adhesion Molecule-1 in Early Diagnosis of Neonatal Infection

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Abstract

Background: Infection is a leading cause of neonatal morbidity and mortality worldwide. Neonatal sepsis, defined as sepsis within the first 28 days of life is estimated to cause 26% of all neonatal deaths worldwide. Diagnosis of the neonatal Infection is difficult, C-reactive protein (CRP) is widely used as a marker of infection; however, its usefulness is limited in the early phase. The role of intracellular adhesion molecule-1 (ICAM-1) has been examined in recent studies as an early marker of neonatal infection with controversial results. **Objective:** The purposes of this study were to determine the usefulness of ICAM-1 in the early diagnosis of neonatal sepsis and the relation of its level to the clinical severity of the disease in comparison with other biomarkers before and after initiation of therapy. **Methodology:** The study consisted of 51 neonates who were chosen from NICU of Damietta General Hospital. The studied neonates were classified into 2 groups: (1) Cases group (n = 34): These were cases with suspected neonatal sepsis. This group was furtherly subdivided according to blood culture into two subgroups: (a) Infected group (n = 23): These were patients with positive blood culture, (b) Not infected group (n = 11): These were patients with negative blood culture. (2) Control group (n = 17): These were neonates who were apparently healthy with negative CRP and blood culture. **Results:** Among the study group and according to the results of blood culture, it was found 23 (68%) out of 34 of the studied neonates had neonatal infection. The mean ICAM-1 levels were found significantly high (415.3±165.3) in the study infected group of neonates (23 out of 34) in comparison with not infected study group (351.5±63.2) and control group (241.5±98.1). **Conclusion:** The ICAM-1 level is increased in neonatal infection and seems to be correlated with its severity. Assessment of ICAM-1, particularly the higher level could be a useful and early marker in neonatal sepsis and it could be used as good indicator of early neonatal infection while the CRP levels within normal range at the time of the sampling.

Key words: Neonatal morbidity, mortality, sepsis, infections

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Neonatal infections remain a frequent and important cause of morbidity and mortality, despite advances in maternal and neonatal care. As many as 2% of fetuses are infected in utero and up to 10% of infants have infections in the 1st month of life[1].

Over recent years, there has been great interest in the potential diagnostic value of a range of hematological and immunological surrogate markers of infection[2,3]. The value of physiological measurements in such context has also recently been examined[4].

The C-reactive protein (CRP) is a component of the innate immune system and increased levels of CRP are observed early in response to severe bacterial infection. As a classical acute phase reactant, however, CRP elevation alone has insufficient specificity for diagnosis of neonatal infection[5].

Soluble intercellular adhesion molecule-1 (sICAM-1) is an adhesion molecule expressed on both alveolar epithelial cells and vascular endothelium[6]. The role of intracellular adhesion molecule-1 (ICAM-1) has been examined in recent studies as an early marker of neonatal infection with controversial results[7]. Adhesion molecules may play a role in the evolution and severity of neonatal sepsis[8].

Because the CRP assessment had been associated with several drawbacks, namely its late appearance and persistence after treatment, a new marker (ICAM-1) should be evaluated for the early diagnosis of sepsis in newborn infants and whether its level is related to the clinical severity of the disease in comparison with other biomarkers as C-reactive protein, blood culture and complete blood picture before and after initiation of therapy.

MATERIALS AND METHODS

The present study is a case control comparative study, which consisted of 51 neonates chosen from NICU of Damietta General Hospital. The studied neonates were classified into 2 groups:

- **Cases group (n = 34):** These were cases with suspected neonatal sepsis. This group was further subdivided according to blood culture into two subgroups:
  - **Infected group (n = 23):** These were patients with positive blood culture
  - **Not infected group (n = 11):** These were patients with negative blood culture
- **Control group (n = 17):** These were neonates who were apparently healthy with negative CRP and blood culture

All studied neonates were subjected to the following:

- **Detailed history taking:** The caretaker of each enrolled neonate was subjected to a pre-designed questionnaire that include the last menstrual period to determine the gestational age, the current age of the baby, risk factors for sepsis as maternal fever, PROM and mode of delivery
- **Thorough clinical examination:** With special emphasis on gestational age determination, weight, head circumference of the baby, signs suggesting neonatal sepsis as poor suckling, disturbed level of consciousness, cyanosis, RD, sclerema and temperature instability. The NICU admission for any suspected neonatal sepsis was done
- **Treatment:** It was initiated until the result of blood culture by using ampicillin (100 mg kg^{-1} day^{-1}) and gentamycin (3 mg kg^{-1} day^{-1})
- **Laboratory investigations:** Complete blood count, semi quantitative CRP, blood culture and sensitivity and serum intercellular adhesion molecules-1 (ICAM-1) by ELISA technique.

Blood culture: Following disinfection of the skin with 70% alcohol, 1 mL venous blood sample was taken and immediately expelled into a test tube containing 5 mL sterile nutrient broth under aseptic condition. The tube is left in the incubator at 37°C for 24 h. Then subcultures on blood agar were done and inoculated both aerobically and anaerobically. Aerobic plates were examined after 24 h for any growth and the same was done after 48 h for anaerobic plates. If no growth was found subcultures were done every 3 days for 3 successive times and if still no growth was seen, cultures were considered negative and excluded. Positive cases were identified using gram staining and biochemical reaction[9]. Serum ICAM-1 estimation: Cell culture supernatant, serum, plasma (EDETA, heparinized) were tested with this assay using ELISA kits.

Statistical analysis: All the study analyses were done by using Statistical Analysis System Software package (SAS, version 9.0). Descriptive analysis (χ^2) test and fisher exact tests, as appropriate, for the categorical variables and t test for the continuous variables). Correlations between studied biomarkers were determined by Pearson's correlation coefficient (r). The ROC curve was used to find out different cut

off points the sensitivity and specificity as well as positive and negative predictor values of ICAM-1. The $p<0.05$ was considered to indicate statistical significance.

RESULTS

In the present study, there were no statistically significant differences between all groups as regard to their gestational age, post-natal age and sex of the neonates, body weight at birth, head circumference and the respiratory rate and mode of delivery. On the other hand, the heart rate of the studied neonates showed a significant difference in all groups ($p = 0.001$) with the lowest rate was among the control group (137 ± 7.0). Also, premature rupture of membrane was present only among the cases group with a significant difference between both groups ($p = 0.04$) (Table 1). Regarding ICAM-1 level, There has been statistically significant difference between the cases and control groups as well as infected and infected groups regarding the mean level of ICAM-1 (415.3 ng mL^{-1} in infected, 351.5 ng mL^{-1} vs 241.5 ng mL^{-1} in control, $p = 0.001$). Positive CRP was more frequent among the infected group than the not infected and control groups (43, 18 and 0%), respectively with statistically significant difference between all groups ($p = 0.003$), but no significant difference between infected and no infected groups ($p = 0.25$). For the other biomarker (leukocytic count), there were no statistically significant differences among all studied neonates except for platelet count where there was a borderline statistically significant difference ($p = 0.05$) between the mean level of platelets in the infected and not infected group (Table 2, 3). In relation to treatment, the mean level of ICAM-1 measured in the cases before and after treatment showed a marked difference as its level was markedly decreased after treatment among both infected and non-infected cases with highly statistically significant difference ($p \leq 0.001$). Also the leukocytic count was lowered after treatment with highly statistically significant difference ($p \leq 0.001$). On the other hand, although, the positive CRP was less frequent after treatment, the deference was not reach statistical significant differences (Table 4).

The prediction accuracy of the ICAM-1 showed great variation according to the used level to detect its sensitivity and specificity. The higher sensitivity (i.e., the ability to pick up those neonates with early neonatal infection) is reached when the level is above 295.5 ng mL^{-1} (sensitivity = 80%). The higher detected specificity (i.e., the ability to exclude those neonates without infection) is reached when the level is above 456.5 ng mL^{-1} (specificity = 91%). Also, the positive predictive value is the highest at this level (>456.5 ng mL^{-1}) (Table 5, Fig. 1).

Table 1: General characteristics of studied newborns

	Cases (n = 34)			
Neonatal characteristics	Infected (n = 23)	Not infected (n = 11)	Control (n = 17)	p-value
Gestational age (weeks) (Mean±SD)	35.9±2.4	35.9±2.9	36.3±1.9	0.86
Age in days (Mean±SD)	3.9±3.7	2.2±3.5	2.2±1.9	0.14
Sex (No. %)				
Male	17 (74%)	8 (73%)	8 (47%)	0.21
Female	6 (26%)	3 (27%)	9 (53%)	
Body weight (g) (Mean±SD)	2511±794	2798±1055	2632±803	0.65
Head circumference (cm) (Mean±SD)	33.9±2.5	34.1±1.4	32.5±2.3	0.1
Respiratory rate (c/min) (Mean±SD)	56.0±13	61.0±17.0	51±10	0.2
Heart rate (b/min) (Mean±SD)	145.0±10	150.0±7.0	137±7	0.001*
Mode of delivery (No. %)				
Caesarean section	14 (61%)	6 (55%)	8 (47%)	0.76
Vaginal delivery	9 (39%)	5 (45%)	9 (53%)	
PROM (>18 h) (No. %)				
No	17 (74.0)	8 (73%)	17 (100%)	0.04*
Yes	6 (26.0)	3 (27%)	0 (0.0%)	

*Significant

Table 2: Comparison of the mean level of ICAM-1 and other biomarkers in the studied neonates (before treatment)

	Cases (n = 34)			
Variables	Infected (n = 23)	Not infected (n = 11)	Control (n = 17)	p-value
ICAM-1 (ng mL^{-1}) (Mean±SD)	415.3±165.3	351.5±63.2	241.5±98.1	0.001*
CRP				
Positive	10 (43%)	2 (18%)	0 (0.0%)	
Negative	13 (57%)	9 (82%)	17 (100%)	0.003*
TLC ($\times 10^3$) (Mean±SD)	14.8±6.1	13.3±4.5	14.1±6.2	0.76

*Significant

Table 3: Comparison of the mean level of ICAM-1 and other biomarkers among the studied cases before treatment

	Cases (n = 34)		
Variable	Infected (n = 23)	Not infected (n = 11)	p-value
ICAM-1 (ng mL^{-1}) (mean±SD)	415.3±165.3	351.5±63.2	0.003*
CRP			
Positive	10 (43.0)	2 (18.0)	0.25
Negative	13 (57.0)	9 (82.0)	
Leukocytic count (×10^3) (Mean±SD)	14.8±6.1	13.3±4.5	0.41
Platelet count (Mean±SD)	167×10^3±72	250×10^3±120	0.05*

Table 4: Comparison of the mean level of ICAM-1 and other biomarkers among the studied neonates before and after treatment

	Cases (n = 34)		
Variables	Before treatment	After treatment	p-value
ICAM-1 (ng mL^{-1}) (Mean±SD)			
Not Infected cases (n = 11)	351.5±63.2	187.0±62.2	<0.001*
Infected cases (n = 23)	415.3±165.3	236.6±65.9	<0.001*
CRP			
Not Infected cases (n = 11)			
Positive	2 (18%)	2 (18%)	1.00
Negative	9 (82%)	9 (82%)	
Infected cases (n = 23)			
Positive	10 (43%)	7 (30%)	0.17
Negative	13 (57%)	16 (70%)	
Leukocytic count (×10^3) (Mean±SD)			
Not Infected cases (n = 11)	13.3±4.5	11.3±2.9	0.001*
Infected cases (n = 23)	14.8±6.1	13.5±4.8	0.001*

*Significant

Table 5: Sensitivity and specificity of ICAM-1 in the detection of early neonatal infection among the cases group (n = 34)

ICAM-1 (ng mL^{-1})	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ICAM-1 (Q1)				
≤295.5	21.00	73.00	63.00	30.00
>295.5	80.00	27.00	69.00	38.00
ICAM-1 (Q2 = median)				
≤345	52.00	45.00	65.00	29.00
>345	52.00	55.00	71.00	35.00
ICAM-1 (Q3)				
≤456.5	65.00	9.00	65.00	11.00
>456.5	35.00	91.00	89.00	40.00

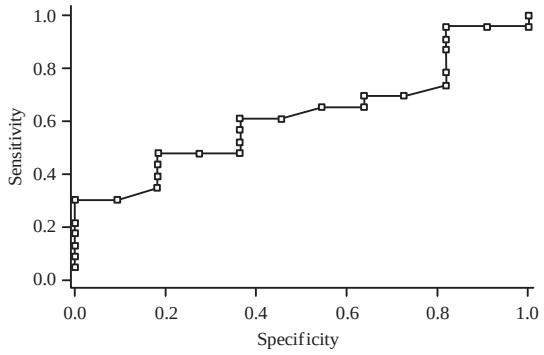

Fig. 1: Estimated Receiver Operator Characteristics (ROC) curve depicting the continuous relationship between sensitivity and specificity points with shifting threshold value of ICAM-1 level in the prediction of early neonatal infection

DISCUSSION

The ICAM-1 is a trans-membrane glycoprotein of the immunoglobulin super-family. It is e expressed on the surface of the endothelial cells, platelets, neutrophils and various other leukocyte subsets[10] shedding of ICAM-1 is thought to promote detachment of leukocytes from the endothelium, thus limiting local inflammation[11]. Since, neonatal sepsis/infection is particularly difficult to diagnose and no dependable predictors exist[12], the present study has been evaluated ICAM-1 as markers for the presence of infection in neonates.

In the present study, there was only 68% had positive blood culture (infected) and this was expected since blood cultures are positive in only 5-10% of suspected sepsis cases, even at highly resourced facilities[13].

The high level of ICAM-1 among infected newborns (with positive blood culture) rather than non-infected (having clinical signs of sepsis with negative blood culture) and control groups is probably due to the release of inflammatory mediators and cytokines in sepsis which induce chemokine secretion from endothelial cells and other vascular cells and increase the expression of cell surface adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1)[14]. On the other hand, positive CRP was less frequent than negative because CRP takes 12-24 h to increase to measurable levels[15]. The present study investigated the role of ICAM-1 with comparison between neonates with either positive or negative blood culture, which might reflects the severity of infection among those neonates.

For the other biomarker (leukocytic count), there were no statistically significant differences among all studied neonates as the results were nearly comparable. Many of these indices are falsely low in a septic neonate and remain very nonspecific and have low positive predictive value. On the other hand, normal WBC counts may be initially observed in as many as 50% of cases of culture-proven sepsis. Infants who are not infected may also demonstrate abnormal WBC counts related to the stress of delivery or several other factors[16]. Furthermore, the platelet count was lower among infected than non infected cases, this is because thrombocytopenia with counts less than 100,000 may occur in neonatal sepsis in response to the cellular products of the microorganisms. It may be a presenting sign and can last as long as 3 weeks. Nonetheless, because of the myriad of causes of thrombocytopenia and its late appearance in neonatal sepsis, the presence of thrombocytopenia does not aid the diagnosis of neonatal sepsis[17].

In relation to treatment, the mean level of ICAM-1 measured in the infected or not infected cases before and after treatment showed a marked difference, as its level was markedly decreased after treatment ($p \leq 0.001$ for each group). This may be attributed to that ICAM-1 seems to be the initial marker of inflammatory reactions and expression of membrane-bound ICAM-1 in inflammatory tissue is upregulated by proinflammatory cytokines such as IFN-γ and tumor necrosis factor α (TNF-α)[18]. Thus, after treatment of infection these proinflamatory cytokines decreased and hence ICAM-1, which means that the level of ICAM-1 is related to the severity of the disease[8]. Furthermore, there was statistical non significant decrease in the level of CRP after treatment among the infected cases and no changes was occurred in the level among the not infected cases, this may be due to that its half life is very long and it takes 5-7 days to normalize after eradication of the infectious agent[16]. Nevertheless, the elevated levels occur within a day, peak at 2-3 days and fall to normal within 5-10 days in neonates who recover[19]. These interesting results open the way for researchers in order to construct studies close follow up of ICAM-1 levels thought the course of infection.

Regarding to leukocytic count, there was a highly statistical significant decrease in the count after treatment among infected and not infected cases. Leukocytosis can be a reaction to various infectious and inflammatory processes. This reaction is mediated by several molecules, which are released or upregulated in response to stimulatory events that include growth or survival factors (e.g., granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, c-kit ligand), adhesion molecules (e.g., CD11b/CD18) and various cytokines (e.g., interleukin-1, interleukin-3, interleukin-6, interleukin-8 and tumor necrosis factor). Thus, after eradication of acute bacterial infections, which is stimulatory events leukocytic count returns to normal[20].

Regarding diagnostic statistics, the prediction accuracy of the ICAM-1 showed great variation according to the used level to detect its sensitivity and specificity. The higher sensitivity is reached when the level is above 295.5 ng mL^{-1} (sensitivity = 80%). The higher detected specificity is reached when the level is above 456.5 ng mL^{-1} (specificity = 91%). Also, the positive predictive value is the highest at this level (>456.5 ng mL^{-1}). The probability of neonatal infection when ICAM-1 level above 456.5 ng mL^{-1} is about 89%. The above description indicates the usefulness of ICAM-1, particularly the higher level in the prediction of early neonatal infection and it could be used as good indicator of early neonatal infection. This agree with the other results which demonstrates that the level of ICAM-1 >300 ng mL^{-1} was a good predictor of neonatal infection[21] and disagree with the results done by Dollner *et al.*[22] stated that ICAM-1 and E-selectin) added no further diagnostic information.

Up till now, several markers including soluble adhesion molecules had been investigated as markers for neonatal infection, however, none of them were introduced in a clinical setting because they did not reach predictive ability[12]. The high predictive value of ICAM-1 level in the present study might be a promising marker for early diagnosis and follow up of neonatal infections.

The ICAM-1 levels among neonates is not affected by ethnicity or gender[23], but increases in asphyxiated low birth weight newborns[24]. There is a lack of studies which evaluated the role of ICAM-1 level among preterm newborns as well as other neonatal disorders.

It is concluded that ICAM-1 ELISA is a 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.

CONCLUSION

The ICAM-1 seems to be an early marker for neonatal infection as it increases early in the course of the disease, while CRP is still within the normal range thus, it may be a good indicator for early infection. Moreover, the significant association between elevated ICAM-1 levels and positive blood culture reflects its correlation with the severity of sepsis. Also, ICAM-1 levels might be used for monitoring response of the infected newborns to treatment, as the decline of ICAM-1 levels in response to treatment was more rapid than CRP levels, which signifies its value in follow up and treatment success. Thus, ICAM-1 may be used in early diagnoses of neonatal sepsis as well as in the follow up of treatment of neonatal sepsis, which can reduce the unnecessary use of antibiotic therapy and early discharge from hospital to avoid nosocomial infections.

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