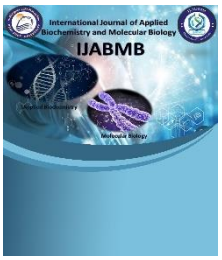
International Journal of Applied Biochemistry and Molecular Biology (IJABMB)



The role of soluble intercellular adhesion molecule_1 (sICAM-1) in the diagnosis of neonatal sepsis

Gamal El_Din Mohamed, M.D. [1], Noha A. Doudar, M.D.[2], Nabila Hashem Abdel Salam, M.B.B.CH. [1] Osama Ezzat Botrous, M.D.[1]

1Paediatrics Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt.
2Clinical Pathology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt.

***Corresponding author:**

Noha A.Doudar

Assistant professor of Clinical and chemical pathology, Faculty of Medicine, Beni-suef University, Beni-suef, Egypt.

E-mail: noha_ad@hotmail.com

Phone number 01001031416

Running Title: sICAM-1 role in the diagnosis of neonatal sepsis

Abstract

Background: One of the leading causes of newborn death and morbidity is still neonatal sepsis. This occurs despite the use of extremely powerful antibiotics and improvements in prenatal and neonatal care. For infants with infections, however, early detection and treatment improve survival.

Objective: The purpose of this study was to assess the diagnostic utility of serum intercellular adhesion molecule-1 (sICAM-1) with other, more well-established methods such as blood culture and c-reactive protein (CRP) for neonatal septicemia.

Patients and methods:

Seventy newborns were split into two groups for our study: Group (A): Fifty full-term and preterm neonates with septicemia. Group (B): As controls, healthy preterm and full-term newborns. In our study, blood cultures were taken as soon as feasible following NICU admission, and the findings indicated that 45 (90%) of sepsis cases had culture-proven sepsis.

Results:

According to our research, group A (the septicaemic group) had greater circulating levels of sICAM-1 than group B (the controls). As a test for early diagnosis of newborn septicemia, sICAM-1 demonstrated 70% sensitivity and 90% specificity at a cut-off value of 147ng/ml in our investigation. In contrast to early-onset sepsis, our study found that s-ICAM-1 was elevated in late-onset sepsis. Poor eating was the most common symptom in the patient groups in our study then trouble breathing and insufficient perfusion.

Conclusion:

We propose that sICAM-1 serum levels are raised during infections and can serve as a neonatal septicemia diagnostic marker.

Keywords: sICAM, neonatal sepsis, full term.

Introduction

Worldwide, sepsis is a leading cause of infant mortality and morbidity, either as a main pathology or because of another condition. International comparisons demonstrate that the burden of infection can be lessened, but even among the most highly developed nations, vulnerable hosts, non-specific clinical presentation, and a constantly shifting pathogen population provide significant challenges (1).

In developing nations, infections account for about 2 million newborn deaths annually. The mortality rate dropped to 5.1 per one thousand live births in other developed nations as a result of developments in Obstetrics alongside neonatal intensive care facilities, as well as increased survival, especially for premature as well as low birth weight newborns who are at a higher risk of sepsis due to their immunological conditions and invasive treatments (2).

Systemic indicators of circulatory compromise, such as pallor, hypotonia, poor peripheral perfusion, and poor responsiveness, are hallmarks of neonatal sepsis, a clinical illness brought on by bacterial bloodstream invasion during the first month of life (3). Neonatal sepsis is a condition that affects critically unwell neonates under one month of age who have positive blood cultures (4).

There are several difficulties in distinguishing sepsis caused by bacteria from other illnesses that frequently affect newborns in an intensive care unit for newborns (5).

According to estimates from the World Healthcare Organization (WHO), neonatal sepsis causes 1 million deaths annually (10% of all deaths in children under five), with 42% of those deaths taking place in their first week after birth (6). Septicaemia may occur after an undetected or insufficiently treated localized infection, or it may be a precursor to infection of a particular organ system (e.g., meningitis or osteomyelitis) (7).

A clinical syndrome known to be severe inflammatory reaction syndrome is defined by at least two of the following symptoms: (1) fever or hypothermia; (2) tachycardia; (3) tachypnoea; and (4) a rise in immature forms or aberrant white blood cells. Sepsis is the name for severe inflammatory response syndrome, which can be caused by a variety of illnesses (8). Even though they are nonspecific, clinical symptoms such as apnoea, food intolerance, and the requirement for more respiratory support are concerning for sepsis caused by bacteria (9).

Abnormal stimulation of the clotting system is often linked to neonatal sepsis, resulting in numerous organ dysfunction syndromes and microcirculatory disruption (10). various nations and eras have various microorganisms linked to newborn sepsis. In many nations, newborn sepsis is most frequently caused by Group B streptococcus (GBS) (11).

Patients and methods

Seventy neonates in the Neonatal Intensive Care Unit (NICU) at Beni-Seuf University Hospital and Beni-Seuf General Hospital participated in this prospective study, which was divided into: Fifty instances with proven sepsis comprise Group A (Patients). Group B was composed of (Controls): 20 healthy newborns who were identical to the patient group in terms of weight, sex, and gestational age and showed no symptoms of acute clinical impairment.

Age (0–28 days), both sexes (male and female), full-term and premature, and the development of acute clinical deterioration as a clinical indicator of newborn septicemia to (early and late onset) are the inclusion criteria. Positive blood culture, CRP ~ 6 mg/dl, and white blood cells > 15000 cells/mm3. Infants with chromosomal abnormalities and congenital defects are excluded.

In addition to the obstetric history, the newborns' antenatal history such as diabetes mellitus, mother's fever 38°C, and maternal a urinary tract), postnatal history (low score on Apgar at one to five minutes, fever, jaundice, etc.), birth history (PROM symptoms, maternal fever, prolonged second stage of labor), and present history (including the most prevalent indications of sepsis) were all examined. Fetal age, anthropometric measurements (weight, length, and head circumference), and the identification of clinical indicators of sepsis, such as circulatory, neurological, GIT, and respiratory dysfunction, are all part of the clinical examination.

Laboratory investigations:

Samples were centrifuged at 1000 x g for 15 minutes after being permitted to clot for 30 minutes in a serum separator tube (SST) containing 5 ml of blood. Samples were kept at -20°C and serum was extracted either immediately or in aliquots. Frequent cycles of freezing and thawing were avoided. Leishmania Giemsa-stained peripheral blood film is used for the differential count in the Complete Blood Count (CBC), which is performed on a coulter to calculate the I/T ratio. A qualitative latex agglutination assay is used in CRP. They performed a blood culture. ELISA was used to measure S-ICAM.

Statistical analysis of the results of the present study were conducted using the mean (x), standard deviation (SD), analysis of variance (ANOVA), independent sample student t-test, and Fisher's exact test.

Results

The demographic data in the studied groups

There was not a statistically significant distinction between the two groups under study, according to the analysis of demographic data comparing the patient and control groups in Figures 1 and 2.

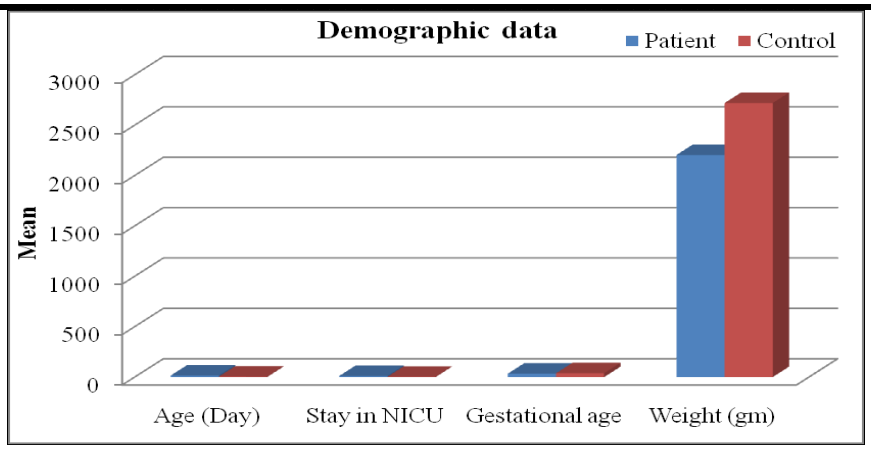


Figure (1): Comparison between patient and control as regarding demographic data

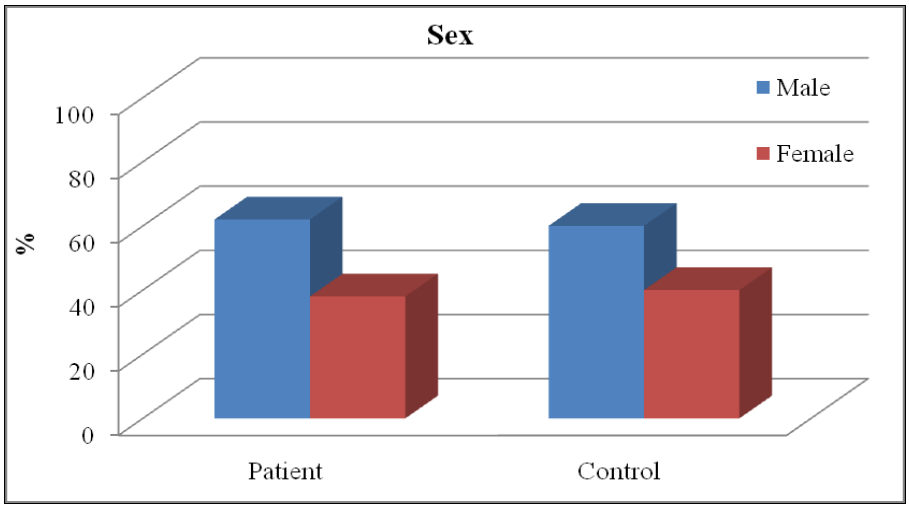


Figure (2): Comparison between patient and control as regarding sex

The clinical data of the patients

Table 1 indicated that whereas heat was less common among patients (6%), poor eating was more common with patients (96%) and RD (84%).

Table (1): Clinical data of the patients

	No.	%
Tachycardia	22	44
Apnea	15	30
Tachypnea	23	46
RD	42	84
Cyanosis	13	26
Bradycardia	6	12
Hypotonia	10	20
Seizures	15	30
Poor perfusion	31	62
Irritability	18	36
Poor feeding	48	96
Hepatomegaly	5	10
Abdominal distention	26	52
Poor skin colour	32	64
Hypothermia	22	44
Hyperthermia	3	6

The laboratory data of the participants

The laboratory results for Hb, Tlc, Plt, and CRP revealed a substantial statistically significant variance among the two groups under study (Table 2). Figure 3 demonstrated that whereas Klebsiella was less common among patients who had staph aureus (2%), it was more common in patients (36%) and controls (24%). According to Figure 4, 8% (4) of the patients had a maternal UTI, 16% (8 patients) suffered maternal hypertension, and 24% (12 patients) suffered maternal PROM.

Table (2): Comparison between patient and control as regarding laboratory investigations

	Patient Mean ± SD	Control Mean ± SD	P value	Sig.
Hb (gm/dl)	14.5±2.8	16.5±1.77	0.004	HS
Tlc (103/cmm)	12.9±8.1	5.8±1.51	0.001	HS
Plt (103/cmm)	160.0±91.5	244.5±45.36	0.001	HS
CRP (mg/dl)	72.1±23.3	4.35±1.27	0.001	HS

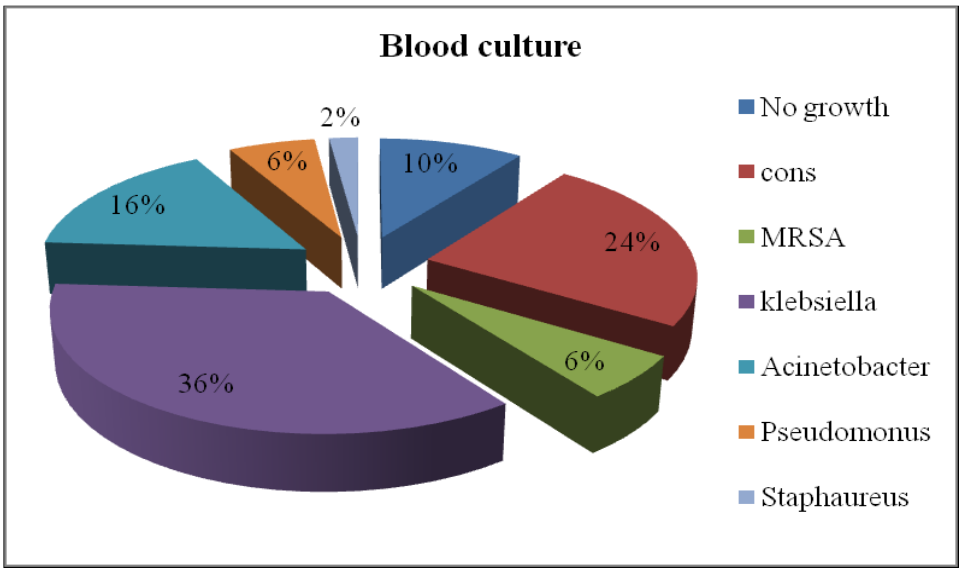


Figure (3): Blood culture in patients' group

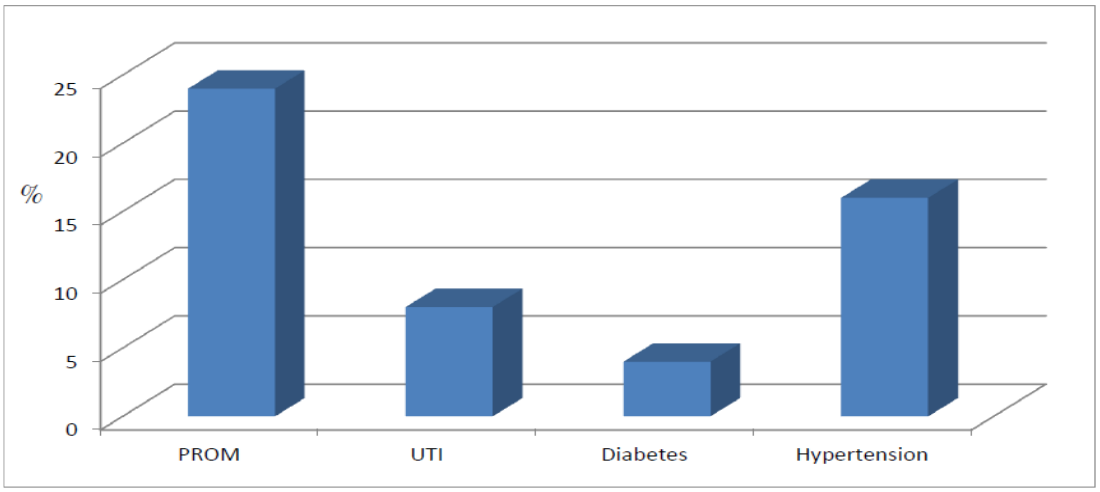


Figure (4): Maternal risk factors in patient group

sICAM-1 levels in the studied groups

Regards sICAM-1, Figure 5 demonstrated a statistically significant variation between the patient and control groups. It is noteworthy that patients had a higher frequency of unusually high levels of sICAM-1 (70%) compared to the control group (10%).

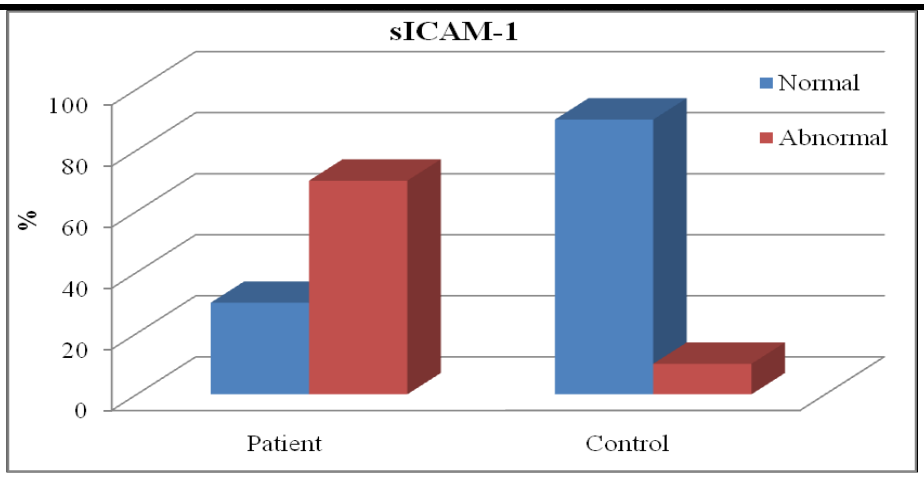


Figure (5): Comparison between patient and control as regarding sICAM-1

The correlations of sICAM-1 with demographic and laboratory data

Table 3 demonstrated a non-significant connection (p-value of >0.05) between sICAM-1 and patient demographic information. The relation between sICAM-1 and patient lab data was not significant (p-value >0.05), as Table 4 demonstrated.

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Table (3): Correlation between sICAM-1 and demographic data in patient

	sICAM-1		P value
	R	P value	
Age (Day)	-0.2	0.135	NS
Stay in NICU (Day)	-0.2	0.184	NS
Gestational age (week)	-0.1	0.533	NS
Weight (gm)	-0.1	0.362	NS

Table (4): Correlation between sICAM-1 and lab. data in patient

	sICAM-1		P value
	r	P value	
Hb	0.1	0.635	NS
Tlc	0.01	0.738	NS
Plt	0.01	0.781	NS
CRP	-0.1	0.378	NS

The Roc curve Analysis of sICAM-1 as a test for early detection of neonatal sepsis

The sensitivity and specificity of sICAM-1 as a patient marker (the capacity of sICAM-1 to differentiate between patients and control) were determined to be 70% sensitivity and 90% specificity, with a cutoff (>147) in Table 5 and Figure 6.

Table (5): Cut off, sensitivity, and specificity of sICAM-1

sICAM-1	Value
Cut off	**>147**
Sensitivity	**70%**
Specificity	**90%**
Positive Predictive Value (+PV)	94.6%
Negative Predictive Value (-PV)	54.6%
Disease prevalence	**71.4%**

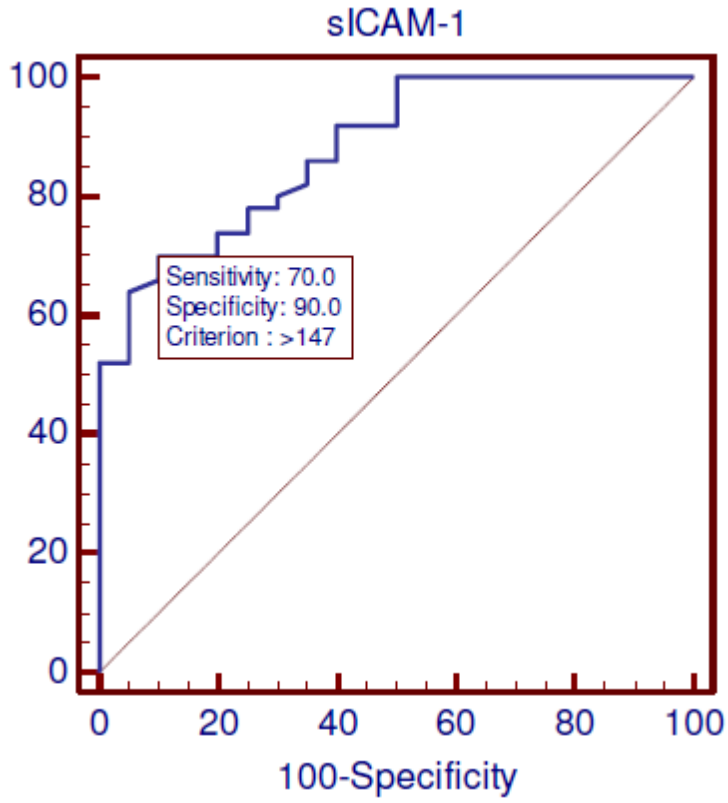

Figure (6): Cut off, sensitivity and specificity of sICAM-1

Discussion

One of the leading causes of newborn death and morbidity is still neonatal sepsis. This occurs despite the use of extremely powerful antibiotics and improvements in prenatal and neonatal care. However, the result for infants with infections is improved by early detection and intervention (12). It is challenging to make the clinical diagnosis of septicemia in newborns due to the lack of distinct symptoms and indicators. There isn't a lab test that has 100% sensitivity and specificity.

The gold-standard method for diagnosis confirmation has been blood culture, although findings are not available until 48–72 hours later (13). Although elevated levels of C reactive protein (CRP), a typical acute phase reactant that is part of the immune system's innate mechanism, are seen within the initial response to extensive bacterial infection, CRP elevation by itself is not specific enough to diagnose neonatal infection (14). The sensitivity for detecting newborn sepsis is limited by the current tests' inability to identify CRP levels that are at the upper range of normal (3–12 mg/dl) (15).

An element of an adhesion cascade that causes leukocyte and platelet aggregation at areas of infection, inflammatory responses, and/or damage is sICAM-1, a cell adhesion molecule that is produced and produced by activated endothelial cells. Additionally, elevated s-ICAM-1 levels have been linked to newborn sepsis in the past and may be useful in diagnosing neonatal infections (16).

The goal of the current study was to elucidate the function of s-ICAM-1 in establishing the presence of neonatal septicemia with other, more well-established metrics such complete blood count, CRP, and blood culture. 50 septicaemic neonates (who underwent an extensive clinical exam and laboratory testing) and 20 neonates without any signs of sepsis served as the control group for our study, which involved 70 babies. In the present investigation, we discovered that most cases (62%) were male neonates.

According to MCIntosh (2002) (17), this is because the X chromosome is linked to antibody synthesis and thymic function. Our research showed that s-ICAM-1 had been greater in late-onset sepsis than in early-onset sepsis, which was consistent with the findings of Salafia et al. (2008) (18), who found that circulating s-ICAM-1 increases significantly from the time of birth to 30 days of life. This fact might reflect the newborn immune system's growth in reaction to environmental factors.

The evaluation of maternal obstetric data in the current study showed that maternal hypertension (16%) and PROM >18 hours (24%) indicated a significant risk factor for neonatal sepsis, even though 48% of those with neonatal septicemia did not have any maternal risk factors. According to research by Kaufman and Fairchild (2004) (19) and Ottolini et al. (2003) (20), maternal UTI was a significant risk factor for newborn sepsis, followed by maternal fever and PROM > 18 hours. According to other research reported by Ramasethu (2004) (22) and Lopez et al. (2003) (21) chorioamnionitis known as was a major risk factor for newborn sepsis.

Additionally, poor eating was the most common symptom in our study's patient group, then breathing problems and poor perfusion. According to a study by Shah (2006) (23) temperature instability, poor eating, and evidence of respiratory distress were the most common symptoms and indicators of sepsis.

Temperature instability and poor eating were the most prevalent clinical indicators in each group of 200 neonates in a study by Hajiehe and Sedigheh (2005) (24) to assess the clinical situation in neonatal sepsis. Neurologic symptoms such as fontanel bulging, drowsiness, and convulsions were more common in the confirmed group. A total of 14 newborns presented with petechiae or mottling on their skin; the confirmed group experienced this condition at a higher rate (47%), compared to the control group (0.7%).

In our study, blood cultures were taken as soon as feasible following NICU admission, and the findings indicated that 45 (90%) of sepsis cases had culture-proven sepsis. In a study conducted in 2005, Betty and Inderpreet discovered that 51.6% of sepsis cases had culture-proven sepsis. However, Procianoy and Silveira's (2004) study (26) discovered that only 21% of sepsis cases had culture-proven sepsis. Because blood cultures might be mistakenly negative in more than 50% of babies, Luck et al. (2002) (27) noted that the actual impact of newborn septicemia as shown by culture-proven events is underestimated.

Additionally, it was noted by (Hsu et al., 2003) (28) that the diagnostic utility of newborn blood cultures is unknown when after delivery maternal antibiotic treatment is implemented. Klebsiella pneumoniae was the most prevalent organism in this study, followed by CONS (36% and 24%, respectively), and bacteria such as MRSA (6%), Staph aureus (2%), pseudomonas (6%).

This is consistent with research by Dzwonek et al. (2008) (29) that found Klebsiella pneumoniae in nearly fifty percent of the positive bloodstream cultures. Klebsiella pneumoniae (37.5%), pseudomonas aeruginosa (30%), Escherichia coli (10%), candida albicans (10%), Staphylococcus aureus (7.5%), and Enterococcus (5%), according to De Bendetti et al. (2007) (30). Klebsiella pneumoniae, Enterobacter, E. coli, and Acinetobacter were shown to be more prevalent in the NICU of Kasr El Eini University Hospital in a prior study (31).

Klebsiella pneumoniae was found in almost half of the positive blood cultures in the study by Dzwonek et al. (2008) (29) that supports this. Escherichia coli (10%), candida albicans (10%), Staphylococcus aureus (7.5%), Enterococcus (5%), Klebsiella pneumoniae (37.5%), and pseudomonas aeruginosa (30%) were all identified by De Bendetti et al. (2007) (30). According to a prior study, Klebsiella pneumoniae, Enterobacter, E. coli, and Acinetobacter were more common in the NICU at Kasr El Eini University Hospital (31).

The levels of s-ICAM-1 in the patients and control groups in the current investigation differed in a highly significant way. This supported the findings of Yan et al.'s (2006) study (33) that neonatal sepsis is linked to elevated levels of s-ICAM-1, s-VCAM, and eselectin in the blood. The study's findings were explained by the theory that endothelium activation occurs during neonatal sepsis.

This discrepancy is like the study by Shapiro et al. (2010) (34) that found that s-ICAM-1, a better indicator of sepsis severity than other markers tested, was linked to endothelium activation in neonatal sepsis, as shown by elevated levels of circulating biomarkers.

Conclusion

Ultimately, we concluded that one of the biggest challenges facing newborn care professionals is the rapid and precise detection of neonatal sepsis. No instances of sepsis are missed or misinterpreted, and the definitive findings of laboratory tests should be accessible a few hours following being suspicious. Although s-ICAM-1 has shown promise in diagnosing newborn sepsis, its widespread use is still constrained by its high cost and challenging laboratory methodology. circulating s-ICAM-1 was greater during newborn infection, and the findings indicate that this can be utilized as a means of diagnosis for neonate septicemia. Our research shows that s-ICAM-1 is a marker associated with stress. It might also control acute inflammation and other elements of host defence. We recommend more research be done on the possible physio pathological, diagnostic, prognostic, and therapeutic roles of s-ICAM-1 in sepsis.

References

1. Roberton N.R.and Rnnie M.J (2001): Infection in the newborn: by Dear P (ed): In Textbook of Neonatology 3rd Edition – Churchil Livingstone p: 1109-1139.
2. Lanari M., papa I., Ventari v, Sermasis. Corvaglia L., Faldella g., and Salvioli Gp.(2001): Neonatal sepsis. Recent: prog Med Nov. 92(11): 690-5.
3. Thaver D, Zaidi AK (2009). Burden of neonatal infections in developing countries: a review of evidence from community-based studies. Pediatr Infect Dis J 28: S3–9.
4. Baltimore RS. (2003): Neonatal sepsis: epidemiology and management.Paediatr Drugs; 5:723.

5. DeCamp L. R, Dempsey A. F, and Tarini B.A. (2009). Neonatal Sepsis: Looking Beyond the Blood Culture: Evaluation of a Study of Universal Primer Polymerase Chain Reaction for Identification of Neonatal SepsisArch Pediatr Adolesc Med. ;163(1):12-14.
6. Lawn JE, Cousens S, Zupan J (2005): 4 million neonatal deaths: when?891–Where? Why? Lancet 365:900.
7. Bellig, L.L. (2004). Neonatal sepsis. (review). Eur. J. Pediatr., 155: 20-126.
8. Chiesa C, Panero A, Osborn JF, Simonetti AF, Pacifico L. (2004): Diagnosis of neonatal sepsis: A clinical and laboratory challenge. Clinical Chemistry; 50 (2): 279-287.
9. DeCamp L. R, Dempsey A. F, and Tarini B.A.(2009).Neonatal Sepsis: Looking Beyond the Blood Culture: Evaluation of a Study of Universal Primer Polymerase Chain Reaction for Identification of Neonatal SepsisArch Pediatr Adolesc Med. ;163(1):12-14.
10. Adel, M.,Awad HA., Abdel-NaimAB., Al-Azizi MM.,(2010). Effects of pentoxifylline on coagulation profile and disseminated intravascular coagulation incidence in Egyptian septic neonates. Journal of Clinical Pharmacy and Therapeutics Volume 35 (3): –257265.
11. Zaidi AK, Thaver D, Ali SA, Khan TA (2009). Pathogens are associated with sepsis in newborns and young infants in developing countries. S10 Pediatr Infect Dis J 28:–18.
12. Stoll BJ and Hansen N. (2003): Infections in VLBW infants: Studies from NICHD Neonatal Network Seminars in Perinatology; 27: 293-301.
13. Ashok K, Yadav C, Wilson P. (2005): Polymerase Chain Reaction in Rapid Diagnosis of Neonatal Sepsis. Indian Ped, Vol. 42_JULY 17.
14. Ng pc (2005): Clinical trials for evaluating diagnostic markers of infection in neonates. Biol Neonate 87:111-2.
15. Himayun M, Ahmad S, Rasool A. (2010): Role of C-Reactive Protein in Early Onset Neonatal sepsis. The Internet Journal of Pediatrics 2. and Neonatology. 20 10 Volume (11) Number.
16. Austgulen R, Arntzen KJ, Haereid PE, Aags, Dollner H (2007): Infection in neonates delivered at term are associated with increased serum levels of ICAM-1 and E-selectin. Acta pediatr 86(3): 274-80.
17. McIntosh N (2002): The newborn in camp bell AGM. McIntosh N editors. Forfar and Arneit's textbook of pediatrics Churchill Livingstone,312:328.
18. Salafia CM, Devore GR, Mainolfi E, Kelly JA, Pezzulo Jc, Rothlein R (2008): circulating Intercellular adhesion molecule-1 in a moniotic fluid, maternal

serum α- Feto protein levels and intrauterine growth retardation. Am J obstet Gynecol 169(4): 830-834.

19. Kaufman D. (2004): Fungal infection in the very low birth weight infant. Current opinion in infectious diseases; 17: 253-259.
20. Ottolini ll1, Lungren K, Cilson S. (2003): Utility of complete blood count and blood culture screening in the diagnosis of neonatal sepsis, Pediatr infect Dis J; 17:.222-235.
21. Lopez-5astre JB, Coto-Cotallo GD, Fernandez CB. (2003): Neonatal invasive candidiasis: A prospective multicenter study of 118 cases. Am Perinatol; 20: 153-63.
22. Ramasethu J. (2004): Thrombocytopenia in the newborn. Curr Hematol Rep; 3: 134-42.
23. Shah GS, Budhathoki S, Das BK, MandaI RN. (2006): Risk factors in early neonatal sepsis. Kathmandu University Medical Journal, Vol. 4, No.2, Issue 14:187-191.
24. Hajiehe Borna, Sedighen Borna (2005): Value of laboratory tests and Creactive proteins in detection of Neonatal sepsis. The Internet Journal of Pediatric and Neonatology. Vol. 5, No. 2.
25. Betty C and Inderpreet S. (2005): Early onset neonatal sepsis. The Indian Journal of Pediatrics; 72 (1): 23-26.
26. Procianoy and Silveira RC. (2004): The role of sample collection tinting on interleukin-6 levels in early-onset neonatal sepsis. J Pediatr (Rio J); 80 (5): 407-10.
27. Luck S, Torny M, d'AgapeyeffK, Pitt A, Heath P, Breathnach A. (2002): Horizontal transmission of Candida parapsilosis candidemia in a neonatal intensive care unit. J Clin Microbiol; 40 (7): 2363--69.
28. HSU KK, Pelton SI , Shaprio DS .(2003): Detection of group B streptococcal bacteremia in simulated intrapartum antimicrobial prophylaxis. Diagn Microbiol Infect Dis; 45: 23-7.
29. Dzwonek AB, Neth O, Thiebaut R, .Gulczynska E, Chilton M, Hellwig T. (2008): The Role of Mannose-Binding Lectin in Susceptibility to Infection in preterm Neonates. Pediatr Res; 63: 680-685.
30. De BK, Smith LG, Owen WE, Roberts WL. (2002): Performance characteristics of an automated high-sensitivity C-reactive protein assay on the Dimension RxL analyzer. Clin. Chim. Acta; 323: 151-155.

31. Badrawi N, Bashir M, Iskander I, Saied D. (2005): Neonatal infection in NICU: magnitude of the problem in NICU of Kasr El-Aini Maternity Hospital. J Kasr EI-Aini medical; 11 (5): 180-195.
32. ShenoiA, Nagesh NK, Maiyapp, Bhat HR, Subba Rao SD. (2006): Multi center randomized placebo-controlled trail of therapy with intravenous immunoglobulin in decreasing mortality due to neonatal sepsis. Ind Pediater; 36:111-38.
33. Yan k, Liaw Pc, Mullington Jm, Shih Sc, Okada H, Bodyak N, Kang Om Toltl, Belikoff B, Buras J, Simms BT, Mizgerd JP, Carmeliet P, Karumanchi SA, Airdwc (2006): Vascular endothelial.
34. Shapiro N1, Fisher C, Donnino M, Cataldol, Tang A, Trzeciak S, Horowitz G, Wolfe RE (2010): E-selectin and intercellular adhesion molecule -1 are released by activated human endothelial cells in neonates. J Emerg Med 39:89-94.