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Significance of Serum Ischemia-Modified Albumin Level as a Marker of Neonatal Sepsis

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ABSTRACT

Background: Neonatal sepsis is a major cause of morbidity and mortality in the neonatal period. Clinical manifestations range from subclinical infection to severe manifestations of focal or systemic disease septic shock. A suitable, economic, sensitive and specific endogenous marker is crucially needed to detect sepsis at an early stage. Objectives: We aimed to identify whether ischemia modified albumin (IMA) level can be used as a marker in the diagnosis of neonatal sepsis and evaluate its prognostic significance.

Methods: A case control study was conducted on 36 newborn babies (18 with neonatal sepsis and 18 without sepsis based on blood culture). Babies were subjected to full medical history, thorough clinical examination and routine laboratory investigations according to our local standards. Serum ischemia modified albumin was measured and correlated to clinical symptoms and prognosis.

Results: There was a significant difference between sepsis group and control group as regards mean serum IMA level (103.7± 31.82 versus 85.36 ± 14.07 ng/ ml) with positive predictive value 80% and negative predictive value 65%.

Conclusion: We concluded that IMA seems to be a useful biomarker for the diagnosis of neonatal sepsis.

Keywords: neonatal sepsis, ischemia modified albumin, neonates, marker.

INTRODUCTION

Sepsis remains a common cause of morbidity and mortality in neonates despite the extraordinary progress in the neonatology field in the recent years [1].

One of the pathophysiological mechanisms of neonatal sepsis is microcirculation insufficiency and the subsequent global tissue hypoxia with further endothelial activation and generalized inflammation .This lead to generalized production of reactive oxygen species (ROS) [2]. Ischemia-modified albumin is the end product of oxidative stress and a form of human serum albumin in which the N-terminal amino acids are unable to bind to transition metal ions. It results from hypoxia, acidosis, free-radical injury and energy-dependent membrane disruption [3].

IMA is accepted as a marker of oxidative stress related to ischemia-reperfusion in different clinical conditions. It has been reported that circulating IMA was associated with inflammation markers because inflammation reduces the capacity of albumin to bind cobalt [4].

The inflammatory response to critical illness in sepsis involves the activation of leukocytes and other inflammatory cells resulting in overproduction of ROS. Neutrophils show a burst of oxygen consumption which is used to generate reactive oxygen species [5].This microenvironment leads to the oxidative modification of several biomolecules such as albumin. The generation of ROS damage the N-terminal region. Albumin's capacity to bind

metals such as nickel, cobalt and copper is diminished and results in IMA [6].

Aim of work

We aimed to identify whether ischemia modified albumin (IMA) level can be used as a marker in the diagnosis of neonatal sepsis and evaluate its prognostic significance**. METHODS:** This study is a case control study, it was conducted in neonatal intensive care unit (NICU) at Zagazig University Hospitals.

Sample size: As mean of ischemia modified albumin level in sepsis group and control groups was 1.47±0.25 and 1.23±0.36 respectively [1]. So sample size was calculated to be 36 (18 in patient group and 18 in control group) using Open Epi program with confidence level 95% and test power 80%.The study was carried out from January 2020 to June 2020.

Inclusion criteria: Newborns with neonatal sepsis based on clinical, laboratory and positive blood culture results.

Exclusion criteria: Acute renal injury and dialysis, abnormal karyotype, suspected congenital metabolic disease, cyanotic congenital heart disease, serious congenital malformation, perinatal asphyxia, maternal diabetes, Intracranial hemorrhage, suspected and diagnosed necrotizing enterocolitis and those treated with indomethacin, ibuprofen and amphotericin B.

Administrative design: The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Approval was obtained From Zagazig University Institutional Review Board (ZU-IRB #5768/9-12-2019). Written informed consent was obtained from caregivers of all babies.

Patients were subject to:

Detailed medical history: Obstetric history to detect risk factors of sepsis as PROM > 18 hours, maternal fever >38 ̊C, maternal UTI, mode of delivery, Apgar score, and symptoms of sepsis as lethargy and poor feeding. Gender, birth weight and gestational age.

Thorough clinical examination: Gestational age assessment using new Ballard score, arthropometric measurements; weight, length and head circumference. Clinical examination for signs of sepsis. Calculation of sepsis score, follow prognosis of cases.

Laboratory investigations: Routine investigations: C-reactive protein (CRP), Complete blood count (CBC), Procalcitonin, blood culture and specific investigations: determination of serum ischemia modified albumin by ELISA.

Statistical Analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 **(**IBM Corp, Armonk, NY**).** Qualitative data were described using number and percentage. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level.

RESULTS

The study revealed that there was significant difference between sepsis and control groups as regards mean serum IMA level (103.7± 31.82 versus 85.36 ±14.07 ng/ml respectively).

Table (1) explains causes of admission in sepsis group and shows that late onset sepsis (LOS) is the most common cause of admission (55.6 %) followed by early onset sepsis (EOS) (33.3 %).

There is significant difference between groups as regards Total leucocyte count, hemoglobin level, CRP and procalcitonin (table 2).

There is significant difference between groups as regard serum IMA level. In sepsis group the mean IMA level was 103.7 ng/ml with a range from 45.27 to 168.8 while in control group, the mean IMA level was 85.36 ng/ml with a range from 59.93 to 115.3 (table 3):

There is no correlation between serum ischemia modified albumin level and prognosis (table 4).

There is no significant difference between IMA level in early and late onset sepsis (table 5).

Results of tables and figures:

Table (1): Illustration of cause of admission in sepsis group:

Cause of admission	sepsis group (n = 18)	
	No.	%
EOS	6	33.3
IUGR, LOS	1	5.6
LOS	10	55.6
LOS e pneumonia	1	5.6

EOS: early onset sepsis, LOS: late onset sepsis, IUGR: intra uterine growth restriction

Table (2): Comparison between the two studied groups according to laboratory investigations:

Laboratory investigations	Sepsis group (n = 18)	Control group (n = 18)	Test of Sig.	P
TLC				
Min. – Max.	2.40 – 28.80	8.20 – 21.0	t= 2.703*	0.013*
Mean ± SD.	16.67 ± 6.78	11.93 ± 3.06		
Median (IQR)	16.55 (12.80 – 22.0)	11.65 (9.70 – 13.0)		
HB				
Min. – Max.	9.50 – 19.0	11.0 – 19.50	t= 2.185*	0.036*
Mean ± SD.	13.65 ± 2.41	15.48 ± 2.62		
Median (IQR)	13.0 (12.50 – 15.20)	16.10 (13.70 – 17.90)		
Platelet x1000				
Min. – Max.	89.0 – 564.0	195.0 – 362.0	t= 0.603	0.553
Mean ± SD.	270.39 ± 125.51	251.0 ± 53.71		
Median (IQR)	241.50 (178.0 – 374.0)	232.0 (211.0 – 282.0)		
CRP				
Min. – Max.	8.0 – 197.0	0.25 – 6.0	U= 0.0*	<0.001*
Mean ± SD.	50.25 ± 45.20	2.93 ± 1.99		
Median (IQR)	46.50 (20.0 – 71.0)	2.60 (0.90 – 5.0)		
Procalcitonin				
Min. – Max.	0.10 – 2.50	0.02 – 0.40	U= 11.50*	<0.001*
Mean ± SD.	0.77 ± 0.56	0.11 ± 0.10		
Median (IQR)	0.69 (0.42 – 1.10)	0.09 (0.04 – 0.10)		

t: Student t-test U: Mann Whitney test, p: p value for comparing between the studied groups *: Statistically significant at $p \leq 0.05$,TLC: total leucocytic count, H:haemoglobin CRP : C-reactive protein

Table (3): Comparison between the two studied groups according to serum IMA level.

IMA	Sepsis group (n = 18)	Control group (n = 18)	T	P
IMA conc ngm/ml				
Min. – Max.	45.27 – 168.8	59.93 – 115.3	2.238*	0.035*
Mean ± SD.	103.7 ± 31.82	85.36 ± 14.07		
Median (IQR)	99.10 (87.10 – 127.09)	87.43 (75.80 – 95.12)		

t: Student t-test , p: p value for comparing between the studied groups , *: Statistically significant at $p \leq 0.05$, IMA: ischemia modified albumin.

Table (4): Relation between IMA level and prognosis in total sample (n = 36):

Prognosis	N	Mean ± SD.	Median	t	p
Improved	28	88.33 ± 17.22	91.87		
Died	7	120.91 ± 39.87	128.80	2.114	0.075
Developed septic hydrocephalus	1	83.91			

Table (5): Difference between IMA level in early onset sepsis and late onset sepsis:

	Number	Mean ± SD	P
Late onset sepsis	12	108 ± 31.9	0.8
Early onset sepsis	6	94.4 ± 32.3	

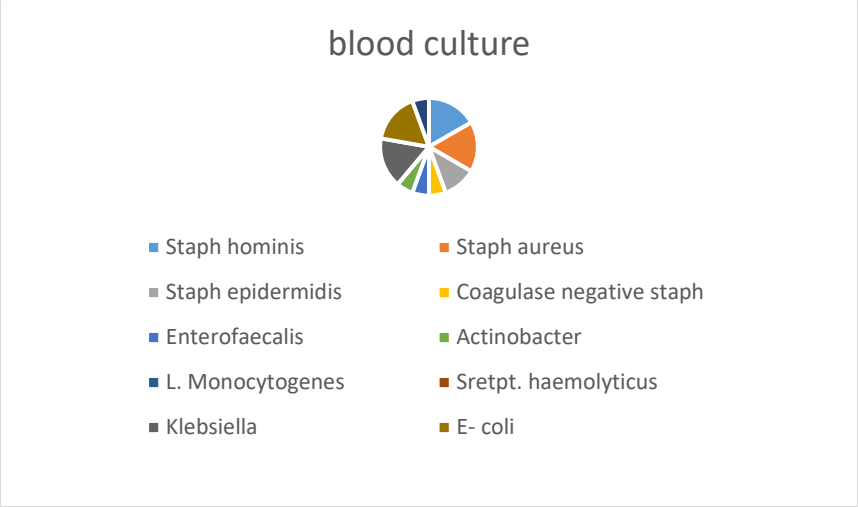

Figure (1): Distribution of sepsis group according to blood culture.

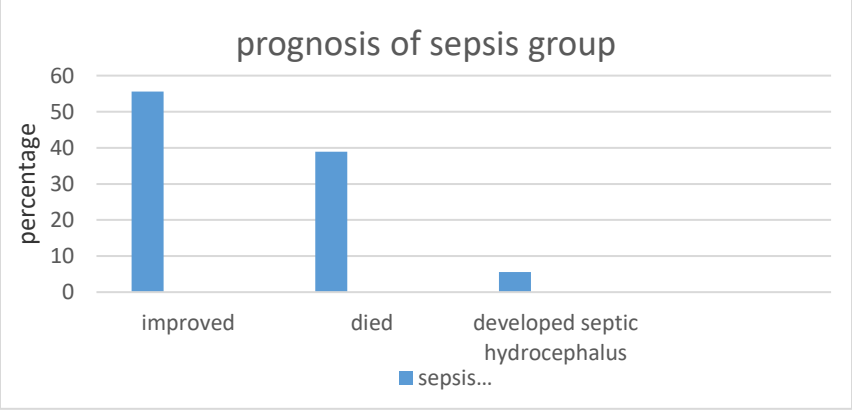

Figure (2): Illustration of prognosis of sepsis group

Figure (1): Shows distribution of sepsis according to blood culture results. 16.7% with Staph aureus, 16.7% with Staph hominis, 16.7% with Klebsiella, 16.7% with Gram -ve bacilli, 11.1% with Staph epidermidis 5.6% with Actinobacter, 5.6% with

Coagulase negative staph , 5.6% with Enterofaecalis and 5.6% with Pseudomonas aueregenosa.

Figure (2): Displays the outcome of sepsis group. 55.6 % of sepsis cases were improved while 38.9 % died and only 5.6 % developed septic hydrocephalus.

DISCUSSION

This study was conducted in Zagazig University Neonatal Intensive Care Units on 36 newborn babies ranging from 31weeks to 38 weeks of gestational age to find out a suitable, economic, sensitive and specific endogenous marker of neonatal sepsis. We divided neonates into 2 groups according to clinical symptoms and blood culture. The first group contains 18 neonates with neonatal sepsis and the second contains 18 control neonates.

Our study showed that the most common cause of admission in sepsis group was LOS (55.6%), followed by EOS (33.3%), then IUGR (5.6%) and LOS with pneumonia (5.6%).

This was in contrast to Demisse et al, [7] in their study to determine patterns of admission in neonatal intensive care unit who found that 59.6% of neonates were EOS while 8.3% had LOS.

Also against, Gudayu et al, [8] who found that 59.33%of cases with EOS while 4.17 % only of LOS.

Results of blood culture in patient group showed that Staph aureus (16.7%), Staph hominis (16.7%), Klebsiella (16.7%) , Gram - ve bacilli (16.7%), with Staph epidermidis(11.1%), Actinobacter (5.6%), with Coagulase negative staph (5.6%), Enterofaecalis (5.6%) and Pseudomonas aueregenosa (5.6%). With totally 61.3% gram positive and 39.7% with gram negative.

These results are in agreement with with a study conducted to determine the causative agent, time to positivity ,and antibiogram of neonatal blood cultures collected in a tertiary care center, Abdelhameed et al., [9] detected 67.06% were Gram-positive, 17.65% were Gram-negative, and 15.29% were fungi (all *Candida*). Coagulase-negative staphylococci were the predominant organism 41.18%.

There is significant difference between groups as regards total leucocyte count, hemoglobin level, CRP and procalcitonin (P value < 0.001).

Similar results were obtained by Zhou et al.,[10] where significant association was found between CRP and positive blood culture results (P= 0.015).

However, the same study found no significant association between leukocyte count and neonatal septicemia.

Our results comes in agreement with El-Mashad et al., [11] who reported a highly significant decrease in hemoglobin level and platelet count in the sepsis group compared with the control group and a high significant increase in total leukocytic count (TLC) and CRP .

Regarding the outcome of sepsis group in our study,10 (55.6 %) improved , 7 (38.9) % died and 1(5.6 %) developed septic hydrocephalus. These results are nearly matched with results of Husada et al.,[12] in their study on late onset sepsis where 84.6% of cases survived and 15.4% died.

There is significant difference between groups as regard serum IMA level. In sepsis group the mean IMA level was 103.7 ng/ml with a range from 45.27 to 168.8 while in control group, the mean IMA level was 85.36 ng/ml with a range from 59.93 to 115.3.

Similar results were obtained by khashana et al.,[13] in their study to detect ischemia modified albumin in early neonatal sepsis where they found Serum levels of IMA were significantly higher in the sepsis group compared to the control group (82.7620.5 vs 24.464.4 ng/ml, p<0.01)

Also our results come in agreement with Yerlikaya et al., [1] in their study to detect serum ischemia-modified albumin levels at diagnosis and during treatment of late-onset neonatal sepsis, detected higher levels in babies with neonatal sepsis which returned to normal after treatment.

Similarly, Kumar et al. [14] detected high levels of IMA in critically ill patients.

We found no correlation between ischemia modified albumin and prognosis. This was in contrast to Yin et al., [3] when they found IMA

as a good predictor of 28 days mortality in patients with sepsis

CONCLUSION

The study concluded that IMA seems to be a useful biomarker for the diagnosis of neonatal sepsis and prediction of its outcome. Larger multicenter studies are still needed to support our findings.

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