DIAGNOSTIC VALUE OF PRESEPSIN IN DETECTION OF EARLY-ONSET NEONATAL SEPSIS

By

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ABSTRACT

Background: *The diagnosis of neonatal sepsis requires careful clinical suspicion, detailed physical examination, and a combination of laboratory tests and radiological tests. Although there isn't one single test that can reliably diagnose sepsis in all neonates, the above combination will establish the diagnosis in most cases.*

Objective: *To evaluate the efficacy of Presepsin in both diagnosis and follow-up of early-onset neonatal sepsis.*

Patients and Methods: *This prospective study aimed to determine the diagnostic utilities [sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)] of Presepsin for early detection of neonatal sepsis, and to define the optimal cutoff value for Presepsin using the receiver operating characteristics (ROC) curve, so that it may be used as a reference with which future studies can be compared. This prospective study had been carried out in the Neonatal Intensive Care Unit at El-Galaa Teaching hospital during the period from October 2018 to April 2019. This study was conducted on 45neonates; 25 cases and 20 healthy neonates were enrolled as a healthy control group.*

Results: *There was significant correlation between both Presepsin and the hematological data (Total leucocytic count, band cells, segmented neutrophils, platelets and immature to total ratio) of the cases. Presepsin had a significant correlation with CRP level which is a laboratory marker of neonatal sepsis. We found that the median level of Presepsin was higher in cases group than control group. ROC curve shows Presepsin value of 0.64 ng/dl was established as a cut off value with 88% sensitivity and 100% specificity. The positive and negative predictive values were 100% and 87%respectively*

Conclusion: *Presepsin is a novel biomarker with high sensitivity and good specificity for sepsis and its measurement can be useful for early diagnosis of neonatal sepsis. Also it was found to be beneficial as a prognostic tool to predict outcome of sepsis in neonatal intensive care and shown to have a correlation with survival.*

Keywords: *Neonatal sepsis, presepsin, C-reactive protein.*

INTRODUCTION

Neonatal sepsis has been defined as bacteremia and accompanying systemic symptoms in the first month of life. **(Darmstadt et al., 2011)**

Despite all the advances in diagnosis and therapy, neonatal sepsis continues to be one of the major causes of morbidity and mortality. **(Polin RA et al., 2015)**

Although the incidence in neonatal period has been reported between 1 and 10 per 1,000 live births, it is higher in developing countries. **(Stronati M et al., 2013)**

The signs and symptoms are nonspecific in early stages of neonatal sepsis. Therefore, the diagnosis of sepsis is usually difficult and can result with delay in the treatment or unnecessary use of antibiotics. **(Cetinkaya M et al., 2009)**

Blood culture is the gold standard for the diagnosis of sepsis in newborns, but the long waiting time for results and the high level of false-negatives that are secondary to insufficient quantity of sample, contamination, and inability to produce microorganism can lead to delays and errors in diagnosis. **(Weinberg et al., 2007)**

Therefore, various biochemical markers are used to aid decision making regarding antibiotic therapy in neonatal sepsis, nevertheless, no current biochemical marker can provide perfect diagnostic accuracy. **(Hedegaard SS et al., 2015)**

Presepsin (P-SEP) or soluble CD14 subtype, is a truncated variant of soluble CD14, Pathogens stimulate P-SEP shedding from the surface of various immune cell types such as monocytes, macrophages and neutrophils. **(Gauthier BR et al., 2014)**

Although its function is still unclear, P-SEP is believed to interact with B and T cells to modulate specific immune responses. **(Rey Nores JE et al., 2013)**

P-SEP has recently been demonstrated to be a reliable diagnostic and prognostic marker of sepsis in adults. **(Shozushima T et al., 2011)**

Preliminary reference values of P-SEP have mainly been evaluated in infants with LOS. **(Topcuoglu S et al., 2015)**

Therefore, we hypothesized that P-SEP might be an accurate biomarker of neonatal sepsis, and might better discriminate between infectious and non-infectious

inflammatory conditions than the currently used biomarkers. To test this hypothesis, we performed a prospective study to evaluate changes in P-SEP serum concentration in newborns with and without possible neonatal sepsis.

AIM OF THE WORK

The aim of this study was to evaluate the efficacy of Presepsin in both diagnosis and follow-up of early-onset neonatal sepsis.

Ethical Concederaion

1. A written informed concent was obtained from paients or their legal guardains.
2. An approval by the local ehical committe was obtained before the study.
3. The auhors declerad no potenial conflicts of interest with respect to the research, authorship, and/or publication of the article.
4. All the data of the patients and results of the study are confidential and the patients have the right to kept it.
5. The authors received no financial support for the research, authorship, and/or publication of his aricle.

PATIENT AND METHODS

Patients: This prospective study had been carried out in the Neonatal Intensive Care Unit of EL-Galaa teaching hospital during the period from October 2018 to April 2019 with the approval of the ethical committee of Neonatal Intensive Care Unit and parents of the neonates. The study was carried on forty five newborns. They met all inclusion and exclusion criteria for enrollment into this study.

They were divided into 2 groups:

Group 1 (cases): include 25 neonates; high risk neonates and possible sepsis.

Group 2 (control): include 20 neonates free from sepsis.

Inclusion criteria:

The case group (high risk neonates and possible sepsis) consist of term neonates with initial suspected bacterial infection (e.g. prolonged rupture of membranes [PROM], chorioamnionitis, and intrapartum maternal fever) and neonatal factors (e.g presence of meconium-stained amniotic fluid, apnea, respiratory problems that required supplemental oxygen, nasal continuous positive airway pressure, and intermittent mandatory ventilation) with or without clinical signs of sepsis. In the control group: the neonates in this group have gestational age matched with the neonates in the

case group, no antibiotics will used, there is no clinical sign of sepsis and there is no history of risk factors.

Exclusion criteria: Antibiotic therapy at admission, serious congenital malformation, admission after first 72 hours of life, or refusal of parental consent.

Methods: All the neonates at this study were subjected to:

Comprehensive history taking include: Antenatal history: maternal age, maternal gravidity and parity, maternal disease (diabetes and hypertension), maternal diabetic control, maternal infection(TORCH infection), maternal medication during this pregnancy, last menstrual period, obstetric history in the form of problems during delivery and premature rupture of membrane. Natal history: gestational age, neonatal sex and date of birth. Postnatal history: respiratory distress and cyanosis (resuscitation data and Apgar score). Family history: congenital anomalies, previous abortion, sibling death and still birth.

Clinical examination for neonates: Assessment of gestational age through analysis of maternal dates and Ballard scores. Assessment of Apgar score at 1 and 5 minutes. Assessment of down score. Assessment of general condition &reflexes (Moro & Suckling). Assessment of vital signs (respiratory rate, heart rate, blood pressure, temperature, and capillary refilling time). Complete examination including cardiac, chest, abdominal and neurological, laying stress on tolerance to oral feeding, abdominal distension, residual gastric aspirate, jaundice, cyanosis and others. Assessment of initial and final diagnosis.

Radiological study: X rays, sonar (cranial or abdominal) and Echo were done according to the cases.

Laboratory investigation: Complete blood count with differential leucocytic count: Complete blood counts with differential and platelet counts were measured at day 1 for all neonates of control group, and at day 1, day3 and day 7for all neonates of case group. The sample was 2 ml of fresh venous blood which collected from peripheral veins of neonates by sterile venipunctures and put in a sterile vacutainer containing K2 EDTA as anticoagulant, complete blood counts were performed electronically. Immature neutrophil count was determined by multiplying the percentage of bands, metamelocytes by the absolute neutrophil count. Immature to total neutrophil ratio

(I/T) was calculated as: (Bands+ metamyelocyte + mylelocytes)/ (segmented neutrophil + bands+ metamyelocyte + myelocytes).

ABG, Na, K and CRP: ABG, serum sodium (S. Na), serum potassium (S. K) and CRP were measured at day 1 for all neonates at control group, and at day 1, day3 and day 7 for all neonates at case group.

Other routine laboratory tests: Liver and kidney function test.

Blood culture; for all neonates.

Presepsin measurement: Presepsin concentration were measured at day 1 for all neonates at control group, and at day 1, day 3, and day 7 for all neonates at the case group using a commercially available ELISA kit supplied by Wuhan fine Biotech co.,China.

Statistical analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter quartile range (IQR) when data was non parametric. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using Chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two groups regarding quantitative data and parametric distribution was done by using Independent t-test while with non-parametric distribution was done by using Mann-Whitney test. The comparison between more than two paired groups regarding quantitative data and parametric distribution was done by using Repeated Measures ANOVA test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. Receiver operating characteristic curve (ROC) was used to assess the best cut off point with its sensitivity, specificity, positive predictive value, negative predictive value and area under curve (AUC) of the studied marker.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: Non significant (NS). P-value < 0.05: Significant (S). P-value < 0.01: Highly significant (HS).

RESULTS

Table (1): Distribution of the studied groups according to gender, gestational age, birth weight and mode of delivery

		Control group No. = 20	cases group No. = 25	Test value	P-value	Sig.
Gender	Male	12 (60%)	12 (48%)	0.643*	0.423	NS
	Female	8 (40%)	13 (52%)			
Gestational age	Mean ± SD	37.55 ± 1.47	37.96 ± 1.21	-1.029•	0.309	NS
Mode of delivery	NVD	12 (60%)	11 (44%)	1.138*	0.286	NS
	CS	8 (40%)	14 (56%)			
Birth weight	Mean ± SD	3.48 ± 0.41	3.22 ± 0.46	2.000•	0.052	NS
	(2.5 – 3)	4 (20.0%)	13 (52.0%)	5.707	0.058	NS
	(> 3 – 3.5)	4 (20.0%)	5 (20.0%)			
	> 3.5	12 (60.0%)	7 (28.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test

This table shows no significant difference between cases and control groups as regards gender, gestational age, mode of delivery and birth weight.

Table (1): Distribution of risk factors in our studied groups

Risk factors	Cases groups	Control groups	Test of sig.	P-value
Free	0(0.0%)	20(100%)	34.435	0.000
Urinary tract infection	3(12%)	0(0.0%)		
Chorioamnionitis	3(12%)	0(0.0%)		
PROM	11(44%)	0(0.0%)		
Vaginitis	3(12%)	0(0.0%)		
Antepartum Hg	5(20%)	0(0.0%)		

This table shows highly significant higher risk factors in cases group than control group.

Table (2): Differences between cases and control groups as regards complete blood count at day 1

Lab result at day 1	Control group No. = 20 Mean ± SD	Cases group No. = 25 Mean ± SD	Test value	P-value	Sig.
Hemoglobin g/dl	16.90 ± 2.34	16.60 ± 2.02	0.462•	0.647	NS
Hematocrit %	56.20 ± 8.92	53.36 ± 7.06	1.193•	0.239	NS
Total leucocytic count X1000	10.7 ±1.6	21.96 ± 6.93	7.101	0.000	HS
Segmented neutrophils %	44.03±4.42	52.4 ± 12.1	2.935	0.005	HS
Band cells %	2.2± 1.20	13.1±2.08	20.801	0.000	HS
Lymphocytes %	44.4± 6.52	27.65± 3.04	-11.411	0.000	HS
Monocytes %	4.34 ± 1.72	6.19 ± 1.2	4.244	0.000	HS
Eosinophils %	1.6± 0.32	2.01± 0.52	3.086	0.004	HS
Basophils %	0.00± 0.00	0.00 ± 0.00	–	–	–
I/T ratio	0.04± 0.14	0.27± 0.12	5.933	0.000	HS
Platelets X 1000	333.70 ± 61.95	235.28 ± 70.93	4.889•	0.000	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test

This table shows significant differences as regards total leucocytic count, band cells %, segmented neutrophils %, monocytes%, eosinophils%, lymphocytes ,% platelets count and I:T ratio beween cases and control groups.

Table (3): Differences between cases and control groups as regards CRP and Presepsin at day 1

Lab result at day 1		Control group No. = 20	Patients group No. = 25	Test value	P-value	Sig.
CRP mg/L	Median (IQR)	3 (2 – 4)	24 (12 – 96)	-5.782≠	0.000	HS
Presepsin ng/ml	Mean ± SD	0.56 ± 0.05	2.73 ± 1.39	-6.944•	0.000	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test

This table shows cases had significant higher level of CRP and Presepsin than control group.

Table (4): Differences between cases and control groups as regards complete blood count at day 3

Lab result at day 3	Control group No. = 20 Mean ± SD	Patients group No. = 25 Mean ± SD	Test value	P-value	Sig.
Hemoglobin g/dl	16.9 ± 2.34	16.79 ± 1.44	0.191	0.850	NS
Hematocrit %	56.2 ± 8.92	52.24 ± 7.46	1.622	0.112	NS
Total leucocytic count X1000	10.7 ±1.6	14.52 ±3.02	5.105	0.000	HS
Segmented neutrophils %	44.03±4.42	48.40± 8.39	2.104	0.041	S
Band cells %	2.2± 1.20	12.52 ± 1.81	21.911	0.000	HS
Lymphocytes %	44.4± 6.52	30.25± 2.43	-10.038	0.000	HS
Monocytes %	4.34 ± 1.72	7.02 ± 0.56	7.338	0.000	HS
Eosinophils %	1.6± 0.32	3.24± 0.5	12.717	0.000	HS
Basophils %	0.00± 0.00	0.00 ± 0.00	–	–	–
I/T ratio	0.04± 0.14	0.25 ± 0.09	6.097	0.000	HS
Platelets X 1000	333.7 ± 61.95	279.6 ± 69.97	2.710	0.010	S

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test

This table shows significant difference beween cases and control groups as regards total leucocytic count, segmented neutrophils %, band cells%, monocytes%, eosinophils% , I:T ratio, lymphocytes% and platelets count.

Table (5): Differences between cases and control groups as regard CRP and Presepsin at day 3

Lab result at day 3		Control group No. = 20	Cases group No. = 25	Test value	P-value	Sig.
CRP	Median (IQR)	3 (2 – 4)	24 (12 – 24)	-5.600	0.000	HS
Presepsin	Mean ± SD	0.56 ± 0.05	2.58 ± 1.08	-8.362	0.000	HS

This table shows cases had significant higher level of CRP and Presepsin than control group.

Table (6): Differences between cases and control groups as regards complete blood count at day 7

Lab result at day 7	Control group No. = 20 Mean ± SD	Cases group No. = 25 Mean ± SD	Test value	P-value	Sig.
Hemoglobin g/dl	16.9 ± 2.34	14.94 ± 2.63	2.604	0.013	S
Hematocrit %	56.2 ± 8.92	52.24 ± 7.46	1.622	0.112	NS
Total leucocytic count X1000	10.7 ±1.6	12.10 ± 2.4	2.239	0.030	S
Segmented neutrophils %	44.03±4.42	47.2± 4.02	2.515	0.016	S
Band cells %	2.2± 1.20	10.41 ± 1.01	24.924	0.000	HS
Lymphocytes %	44.4± 6.52	38.01± 5.21	-3.656	0.001	HS
Monocytes %	4.34 ± 1.72	4.01 ± 0.51	-0.913	0.367	NS
Eosinophils %	1.6± 0.32	2.20 ± 0.48	4.797	0.000	HS
Basophils %	0.00± 0.00	0.00 ± 0.00	–	–	–
I/T ratio	0.04± 0.14	0.22 ± 0.05	5.983	0.000	HS
Platelets X 1000	333.7 ± 61.95	282.8 ± 104.06	1.929	0.060	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test

This table shows significant difference between cases and control groups as regards total leucocytic count, eosinophils %, band cells %, segmented neutrophils % , I:T ratio, lymphocytes and hemoglobin level.

Table (7): Differences between cases and control group as regards CRP and Presepsin at day 7

Lab result at day 7		Control group No. = 20	Cases group No. = 25	Test value	P-value	Sig.
CRP	Median (IQR)	3 (2 – 4)	12 (6 – 24)	-5.427	0.000	HS
Presepsin	Mean ± SD	0.56 ± 0.05	2.25 ± 1.69	-4.465	0.000	HS

This table shows cases had significant higher level of CRP and Presepsin than control group.

Table (8): Correlation between Presepsin with gender, mode of delivery and birth weight at day 1, day 3 and day 7 in our studied cases.

	Presepsin		
	Day 1	**Day 3**	**Day 7**
	Mean ±SD	**Mean ±SD**	**Mean ±SD**
Gender			
Male	2.46 ± 1.64	2.29 ± 1.29	1.85 ± 1.59
Female	2.97 ± 1.14	2.85 ± 0.8	2.61 ± 1.76
T	0.902	1.332	1.123
P value	0.376	0.566	0.273
Mode of delivery			
NVD	2.87 ± 1.4	2.54 ± 1	1.9 ± 1.38
CS	2.62 ± 1.43	2.62 ± 1.17	2.52 ± 1.9
T	0.442	-0.184	-0.900
P value	0.663	0.856	0.378
Birth weight			
2.5- 3	2.8 ± 1.49	2.56 ± 1.09	2.03 ± 1.42
> 3 – 3.5	2.06 ± 1.15	1.92 ± 1.49	2.1 ± 2.3
> 3.5	3.07 ± 1.39	3.1 ± 0.36	2.76 ± 1.84
T	0.781	1.878	0.429
P value	0.470	0.177	0.656

This table shows that there is no significant correlation between Presepsin with gender, mode of delivery and birth weight at day 1, day 3 and day 7.

Table (9): Correlation between Presepsin with complete blood count at day 1, day 3 and day 7 in our studied cases

	Presepsin					
	Day 1		Day 3		Day 7	
	R	P-value	R	P-value	R	P-value
Hemoglobin g/dl	**-0.561****	**0.004**	**-0.434***	**0.030**	**-0.480***	**0.015**
Hematocrit %	**-0.533****	**0.006**	**-0.797****	**0.000**	**-.699****	**0.000**
Total leucocytic count X1000	**0.816****	**0.000**	**0.560****	**0.004**	0.139	0.506
Segmented neutrophils %	**0.681****	**0.000**	**0.472***	**0.017**	**0.548****	**0.005**
Band cells %	**0.659****	**0.000**	0.204	0.327	**-0.414***	**0.040**
Lymphocytes %	**0.552****	**0.004**	**0.546****	**0.005**	**0.573****	**0.003**
Monocytes %	**0.543****	**0.005**	0.326	0.111	0.189	0.366
Eosinophils %	0.198	0.343	-0.256	0.216	0.227	0.276
Basophils %	-	-	-	-	-	-
I/T ratio	**-0.406***	**0.044**	**0.534****	**0.004**	**-0.474***	**0.017**
Platelets X 1000	**-0.475***	**0.049**	-0.258	0.214	**-0.625****	**0.001**

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
Spearman correlation coefficient

This table shows significant correlation between Presepsin with hemoglobin, hematocrit, total leucocytic count, band cells %, segmented neutrophils %, lymphocytes %, monocytes %, I/T raio, monocytes % and platelats.

Table (10): Correlation between Presepsin with CRP at day 1, day 3 and day 7in our studied cases.

	Presepsin					
	Day 1		Day 3		Day 7	
	r	P-value	r	P-value	R	P-value
CRP	**0.782****	**0.000**	0.168	0.421	**0.681****	**0.000**

This table shows significant statistical difference between the CRP level of the cases group and Presepsin level at day 1 and day 7.

Table (12): Difference between the cases and the control groups in the mean level of Presepsin levels at day 1, day 3 and day 7

Presepsin	Control group No. = 20 Mean ± SD	Cases group No. = 25 Mean ± SD	Test value•	P-value	Sig.
At day 1 Mean ± SD	0.56 ± 0.05	2.73 ± 1.39	-6.944	0.000	HS
At day 3 Mean ± SD	0.56 ± 0.05	2.58 ± 1.08	-8.362	0.000	HS
At day 7 Mean ± SD	0.56 ± 0.05	2.25 ± 1.69	-4.465	0.000	HS

This table shows there is highly significant difference of the mean level of Prespsin between cases and control groups at day 1, day 3 and day 7.

Table (13): Comparison between the culture results of the cases and the Presepsin levels at day 1, day 3 and day 7.

	Culture		P value
	Positive	Negative	
	Median (Min-Max)	Median (Min-Max)	
Presepsin at day 1	3.03 ± 1.2(1.2 – 4.5)	0.52 ± 0.09(0.45 – 0.62)	0.002
Presepsin at day 3	2.87 ± 0.78(1.5 – 4.5)	0.48 ± 0.1(0.4 – 0.6)	0.000
Presepsin at day 7	2.48 ± 1.66(0.9 – 6.1)	0.51 ± 0.09(0.42 – 0.6)	0.056

This table shows there was significant difference as regards the Presepsin level at day 1 and day 3 between positive and negative cultures and was noticed that the median level of the marker at day 1, day 3 and day 7 at the positive cultures were higher than the negative cultures.

Table (14): Mean level of Presepsin in our cases according to final diagnosis.

Final diagnosis	Presepsin		
	Day 1	Day 3	Day 7
	Mean ±SD	Mean ±SD	Mean ±SD
Transient Tachypnea of newborn	2.91 ± 1.18	2.65 ± 0.84	2.21 ± 1.54
Meconium aspiration syndrome	2.17 ± 1.59	2.32 ± 1.23	2.27 ± 1.88
Congenital pneumonia	3.80 ± 0.42	3.85 ± 0.92	3.95 ± 3.04
Neonatal sepsis	2.36 ± 2.46	1.90 ± 1.84	1.20 ± 0.85
IDM	4.10 ± 0.00	3.20 ± 0.00	1.80 ± 0.00
PPHN	3.10 ± 0.00	2.50 ± 0.00	1.50 ± 0.00
Test value	0.752	0.871	0.56
p-value	0.595	0.519	0.729
Sig	NS	NS	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Independent t-test

This table shows no relation between the mean level of Presepsin and the diagnosis of cases.

Table (15): The clinical characteristics of the cases as regard the outcome.

Outcome	Patients group
	No. (%)
Discharged	16 (64.0%)
Died	9 (36.0%)

As regards the outcome of the patients 16 (64.0%) were discharged and 9 (36.0%) were dead.

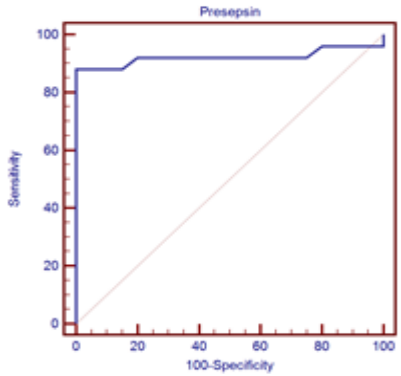

Figure (1): Roc curve of Presepsin at day 1

Table (16): Sensitivity and Specificity of Presepsin at day 1

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>0.64	0.922	88.00	100.00	100.0	87.0

This table shows highly significant higher sensitivity and specificity of Presepsin at day 1.

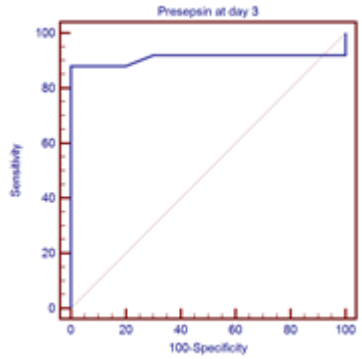

Figure (2): Roc curve of Presepsin at day 3.

Table (17): Sensitivity and Specificity of Presepsin at day 3

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>0.64	0.910	88.00	100.00	100.0	87.0

This table shows highly significant higher sensitivity and specificity of Presepsin at day 3.

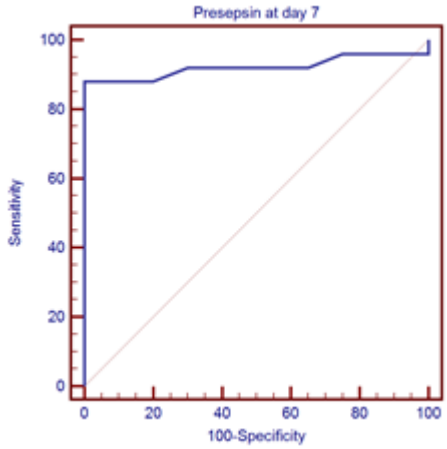

Figure (3): Roc curve of Prespsin at day 7

Table (18): Sensitivity and Specificity of Presepsin at day 7

Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>0.64	0.922	88.00	100.00	100.0	87.0

This table shows highly significant higher sensitivity and specificity of Presepsin at day 7.

DISCUSSION

Sepsis, severe sepsis and septic shock are unquestionably some of the major healthcare problems, affecting millions of people each year worldwide **(Dombrovskiy et al., 2007)**. Prompt diagnosis and treatment with appropriate antimicrobial chemotherapy is of utmost importance in reducing morbidity and mortality associated with sepsis **(Balci et al., 2007)**.

Sepsis is a systemic deleterious host response to infection, possibly leading to severe sepsis (acute organ dysfunction secondary to documented or suspected infection) or septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation). According to the most recent guidelines, published by the Surviving Sepsis Campaign, early recognition of these conditions and speed and appropriateness of therapy in the initial hours after presentation considerably influence the outcomes of septic patients. **(Dellinger et al., 2013)**

Blood culture is the gold standard method for detecting the presence of microorganism in the bloodstream. However, it has

limited usefulness for early detection of infection because it usually requires several days for results to be known. Blood culture may also be plagued by some false negative cases, especially in patients undergoing antibiotic therapy. This can lead to a delay in antibiotic administration and consequently to increased mortality. (Romualdo et al., 2014)

In conclusion, sensitive biomarkers are needed for diagnosis and prognosis of sepsis, severe sepsis and septic shock, particularly in such cases of atypical presentations **(Hausfater, 2014)**.

Cluster of differentiation 14 (CD14) is a glycoprotein expressed on the membrane surface of monocytes and macrophages (mCD14) and serves as a high-affinity receptor for complexes of lipopolysaccharides (LPSs), a compound from the outer cell wall of Gram-negative bacteria, and LPS-binding proteins (LPBs). **(Romualdo et al., 2014)**

Membrane CD14 may also function as a receptor for peptidoglycan, a cell wall component of Gram-positive and some Gram-negative bacteria **(Romualdo et al., 2014)**.

Presepsin is normally present in very low concentrations in the serum of healthy individuals and has been shown to increase in response to bacterial infections, according to the severity of the disease; however, information about Presepsin concentrations in specific populations are very poor **(Shozushima et al., 2011)**.

In this study 45 neonates included at El Galaa teaching hospital from October 2018 to April 2019, subdivided into two groups: 25 neonates which is the case group (high risk neonates and possible sepsis) and 20 neonates which is the control group.

In the case group, 52% females & 48% males and 40% females & 60% males in the control group.

No male predominance in neonatal sepsis was obviously seen in the present study. This agrees with Giavarina & **Mariarosa C. (2014)**, and disagree with the study of **Shaheen A (2008)**; **klein HK (2009)** recorded that male infants had increased risk to develop sepsis more than female infants. A gene located on X chromosome and involved with the function of the thymus or with synthesis of immunoglobulin has been postulated to exist, thus the female has a greater resistance to infection.

The most prominent signs of neonatal sepsis in this study were poor suckling, mottled skin, respiratory distress, poor moro, lethargy and abdominal distension.

Premature rupture of membrane (PROM) was the most important risk factor of neonatal sepsis in this study accounted for 44% of studied cases. This agrees with **(Ng et al., 2009)** who have reported that PROM is a strong risk factor for neonatal sepsis.

In this study, we found that positive history of maternal fever was present in about (15%) of studied cases due to maternal infection. This agrees with **Fjaertoft et al., (2010)** who had noted that maternal fever due to maternal infections like chorioamnionitis and urinary tract infection accounts 20% of neonatal sepsis group.

Our study showed that the percentage of sepsis was high in neonates born by cesarean section than by vaginal delivery with no statistically significant difference. This may be due to increased number of cesarean section than vaginal delivery. This result was in agreement with **(Kayiga et al., 2018)** who revealed that the mode of delivery did not have a statistically significant impact on perinatal mortality. Cesarean delivery was associated with more adverse pregnancy outcomes including sepsis compared to vaginal route of delivery.

From the variable results obtained from different studies, it is evident that the causative organisms causing neonatal sepsis vary from nursery to nursery, between different geographical areas and in the same area with time. Therefore infection control in each hospital should adjust their antibiotics accordingly.

A high statistical significant difference was shown between studied cases and control as regards total leucocytic count, Immature/Total neutrophils ratios, CRP and platelets count. This is in concordance with study done by **Wang et al. (2014)** and **Dalia A. Saied., (2017)** who found that sepsis episodes were characterized by significantly higher total leucocytic count, and Immature/ Total neutrophils ratios, compared with non-septic episodes, as well as lower platelets counts.

Our study showed that there was a highly significant statistical difference between the cases and the control groups as regards the Presepsin level at day 1, day 3 and day 7.

This result was in agreement with a various studies which found a highly significant statistical difference in the mean level of

Presepsin between cases and control groups. **(Chenevier-Gobeaux et al., 2014**, **Pizzolato et al., 2014**, **Yeagashi et al., 2005** & **Shozushima et al., 2011)**.

Małgorzata & Co workers in their study which was conducted on neonates found that Presepsin concentration is significantly increased in both septic neonates and neonates with local infections, independently of their gender, fetal maturity, birth asphyxia and mode of mother's deliver **(Małgorzata et al., 2015)**.

This was agreed by another study on late onset sepsis **(Topcuoglu et al., 2015)**.

Our study revealed that there was non-significant statistical difference between the gestational age of the cases group and Presepsin level at day 1, day 3 and day 7.

This result was in concordance with several studies found that there is no correlation between the Presepsin levels and the gestational age **(Pugni et al., 2015**, **Topcuoglu et al., 2015** & **Mussap et al., 2012)**.

Also we found that there was a non- significant statistical difference between the males and females of the cases group as regards the presepsin level at day 1, day 3 and day 7.

This goes in agreement with three studies which revealed that the median Presepsin concentrations were not significantly different in males in comparison to females **(Chenevier-Gobeaux et al., 2014, Giavarina & Mariarosa C. 2014** & **Małgorzata et al., 2015)**.

The present study showed that the Presepsin level in the cases group at day 1 was more than its level at day 3, and at day 3 more than its level at day 7 despite that the P value has no statistical significance.

This result was in concordance with a study which was carried out on adult patients who have infection. This study revealed that Presepsin values were significantly higher at T0 (first medical evaluation) than at T1 (24 h after admission) and T2 (72 h after the admission) **(Ulla et al., 2013)**. Similary Topcuoglu & Co workers found in a study which were conducted on preterm neonates who were suffering from late onset sepsis that initial Presepsin value were significantly higher than the values measured on the third day of sepsis. Similarly, values measured on the seventh day of sepsis were significantly lower than those measured on the third day. They concluded that decreased

Presepsin denotes a favorable response, indicating that infection has been controlled. **(Topcuoglu et al., 2015)**

Also Poggi & Coworkers reported that Presepsin decreased even on the first day of treatment. His study was conducted on preterm neonates with late onset sepsis. These findings suggest that Presepsin may also be useful for monitoring the clinical response to therapeutic interventions before obtaining culture results **(Poggi et al., 2015)**.

On the contrary Tong et al., in their study which conducted on neonates found that Presepsin level at day 3 more than the level at day 1 (2015).

We observed that there was a significant statistical correlation between the Presepsin level at day 1, day 3 and day 7 with hemoglobin and hematocrit in cases group, also there was significant statistical correlation between the Presepsin level with the total leucocytic count and segmented neutrophils % at day 1 and day 3 and platelets at day 7 of the cases group.

Małgorzata & Co workers found that the increase of Presepsin concentration in septic newborns significantly correlates with the decrease of hemoglobin, hematocrit value and platelets counts. **(Małgorzata et al., 2015)**

There was a significant statistical correlation between the CRP level of the cases group and Presepsin level at day 1 and day 7.

This result goes in agreement with a study on septic newborns which concluded that there is a positive correlation between Presepsin concentrations and CRP in septic newborns **(Małgorzata et al., 2015)**.

Similarly, Chenevier-Gobeaux & Coworkers reached the same result in a study that was conducted on adults **(Chenevier-Gobeaux et al., 2014)**.

The present study showed that there was a non-significant statistical difference between the diagnosis of the cases group and Presepsin level at day 1, day 3 and day 7.

Also Ulla & Coworkers study revealed that Presepsin concentrations in adults did not correlate significantly with the primary site of infection (urinary tract, lung, abdomen, skin, central venous catheter-related, CNS or oral). This was probably due to the fact that Presepsin is produced systemically by circulating cells, not within a specific organ or body area **(Ulla et al., 2013)**.

Our study showed a significant difference as regards the Prespsin at day 1 and day 7 between patient who lived and those who died.

It was noticed that median levels of the markers at day3 and day 7 were higher among the patients who have died.

This was in agreement with Pizzolato & Coworkers mentioned in their review study the correlation between Presepsin serum values with mortality. **(Pizzolato et al., 2014)**

On the contrary two studies which found no difference between the Presepsin levels of neonates who died from late onset sepsis and the survivors **(Topcuoglu et al., 2015** &**Behnes et al., 2015)**.

Other studies, which were conducted on neonatal patients, showed that Presepsin is a novel biomarker with high sensitivity and good specificity for sepsis **(Pizzolato et al., 2014** & **Małgorzata et al.2015)**.

Moreover, Topcuoglu & coworkers stated that in neonates a Presepsin value of 0.85 ng/mL was established as a cut-off value with 67% sensitivity and 100% specificity. The positive and negative predictive values were 100% and 74% respectively **(Topcuoglu et al., 2015)**.

Some systematic reviews and meta-analyses which were carried on adult population showed that the AUC were around 0.85 indicating that the Presepsin had a moderate diagnostic efficiency with high rate of missed diagnosis of around (17%) and misdiagnosis around (19%), and insufficient to rule out or confirm sepsis when used as the only diagnostic test **(Zhang et al., 2015**, **Zheng et al., 2015** & **Tong et al., 2015)**.

Our study showed that a Presepsin value of 0.64 ng/dl was established as a cut off value with 88% sensitivity and 100% specificity. The positive and negative predictive values were 100% and 87% respectively.

CONCLUSION

Presepsin was proven to increase significantly in neonates with neonatal sepsis, Presepsin continues to rise during the first 24 hours reaching higher levels with higher sensitivity and specificity, Presepsin was not affected by gender, Presepsin can predict the prognosis of the patients in the neonatal intensive care unit, early diagnosis of neonatal sepsis cannot rely on a single laboratory test and clinical decision remains to have the upper hand in the diagnosis, also it was found to be beneficial as a prognostic tool to

predict outcome of sepsis in neonatal intensive care and shown to have a correlation with survival.

RECOMMENDATION

Presepsin is a reliable test for early detection of neonatal sepsis. Presepsin can be considered as early specific detector for neonatal sepsis. Since its level rises during the first 24 hours, it can be useful for initiation of antibiotic therapy till results of blood culture are available. Further studies on a larger number of patients are required for more comprehensive statistical analysis and better conclusions. More studies are required for studying the use of presepsin as a sepsis marker in the discrimination between gram negative and gram positive infection. More work is needed to define the association between presepsin and the response to antimicrobial therapy in the clinical setting.

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القيمة التشخيصية للبريسبسن في الإكتشاف المبكر للإنتان الدموي لدي الأطفال حديثي الولادة

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يعتمد تشخيص عدوي الأطفال حديثي الولادة علي عدة عوامل منها التنبؤ الاكلينيكي الدقيق مع الفحص الظاهري الكامل هذا بالاضافه الي نتائج الاختبارات المعملية والأنواع المختلفة من الفحص بالأشعة وبالرغم من عدم وجود اختبار واحد يشخص هذا المرض إلا ان العوامل السابق ذكرها مجتمعة تشخص هذا المرض في معظم الحالات.

والهدف من البحث هو تقييم الدلالات التشخيصية لمتوسط مستوي البريسيبسن عند حديثي الولادة ومعرفة القيمة التي يكون عندها متوسط مستوي البريسيبسن مرجعًا للدراسات التالية وكذلك الحد من إعطاء المضادات الحيوية للأطفال الغير مصابين بالعدوي المبكرة.

هذه الدراسة المحتملة تم إجرائها في وحدة الأطفال حديثي الولادة بمستشفي الجلاء التعليمي في الفترة من شهر أكتوبر ٢٠١٨ حتي شهر أبريل ٢٠١٩ وتضمنت هذه الدراسة مجموعتان: المجموعة الأولي تشمل ٢٥ طفلا مشتبه إصابتهم

بالعدوي المبكرة و المجموعه الثانية تشمل ٢٠ من الأطفال الأصحاء كمجموعة ضابطة.

وقد خضع الأطفال في المجموعتين للإجراءات التالية: أخذ التاريخ المرضي: قبل الولادة وأثناء الولادة وما بعد الولادة مع التأكيد علي العمر الرحمي و جنس المولود و العمر بعد الولادة و مقياس أبجار و إحتياجاتهم من الأكسجين وعوامل الخطورة للأم مثل الوضع السفلي للمشيمة وتمزق الأغشية الحامية للطفل قبل ميعاد الولادة بما لا يقل عن ١٨ ساعة ،كما خضع الأطفال من المجموعتين للفحص الإكلينيكي (السريري) الكامل مع التأكيد علي العمر الرحمي والعلامات الحيوية وتقبل التغذية وما إذا كان هناك إنتفاخ في البطن أو قئ و وجود يرقان أو زرقة وملاحظة الإنعكاسات العصبية لدي الأطفال.

وقد خضع الأطفال الفحوصات التالية: صورة دم كاملة مع عد تفاضلي لكرات الدم البيضاء وقياس مستوي الصوديوم والبوتاسيوم بالدم و قياس غازات الدم و قياس مستوي بروتين سي التفاعلي وأشعة سينية علي الصدر مع عمل فحص بالأنواع المختلفة من الأشعة عند الإحتياج وكذلك قياس مستوي البريسيبسن بالدم عن طريق مقايسة الإمتصاصية المناعية للإنزيم المرتبط ويتم القياس عند اليوم الاول والثالث والسابع للولادة.

وقد أظهرت الدراسة التالي أن متوسط مستوى البريسيبسن بالدم أعلي عند الأطفال المصابين بالعدوى المبكرة

عن متوسط مستواه في أقرانهم الأصحاء وان منحني التحليل الإحصائي لتوقع التسمم الدموي بإستخدام البريسيبسن أظهر ان دقة التحليل قوية وعند قيمة ٠,٦٤نانوجرام/ديسيلتر وكانت الحساسيه ٨٨٪ والتخصصية ١٠٠٪ ونسبة التوقعية الايجابية ١٠٠٪ ونسبة التوقعية السلبية ٨٧ ٪

وقد أظهرت الدراسة أن تمزق الأغشية الجنينية المبكر قبل الولادة لأكثر من ١٨ ساعة كان عامل الخطر الأكثر أهمية للإنتان الوليدي في هذه الدراسة، كما أظهرت الدراسة انه لا يوجد فرقًا كبيرًا ذو دلالة احصائية بين الأطفال المصابون بالعدوي المبكرة والأطفال الأصحاء فيما يتعلق بالجنس وعمر الحمل وطريقة الولادة ووزن الولادة.

كما توضح هذه الدراسة أن الأطفال المصابون بالعدوي المبكرة كان بهم نسبة كبيرة من العدد الكلي لخلايا الدم البيضاء والخلايا المتعادلة والخلايا المتعادلة الأطرية والخلايا المجزأة و نسبة الخلايا الغير ناضجة للعدد الكلي للخلايا المتعادلة و بروتين سي التفاعلي مقارنة بأقرانهم الأصحاء في اليوم الأول و الثالث والسابع للولادة وتوضح أيضًا أن الأطفال المصابون بالعدوي المبكرة بهم عدد أقل من الصفائح الدموية بشكل ملحوظ مقارنةً باقرانهم الأصحاء في اليوم الأول والثالث والسابع للولادة، كما أظهرت الدراسة أيضًا أن متوسط مستوي البريسيبسن كان أعلى في الأطفال المصابون بالعدوي المبكرة مقارنة باقرانهم الأصحاء و لم يكن هناك ترابط ذو دلالة احصائية بين متوسط مستوي البريسيبسن

مع الجنس وطريقة الولادة ووزن الطفل عند الولادة في اليوم الأول و الثالث والسابع للولادة.

كما توضح هذه الدراسة وجود ترابط ذو دلالة إحصائية بين البريسيبسن مع الهيموجلوبين والهيماتوكريت و العدد الكلي لخلايا الدم البيضاءو الخلايا المجزأة والخلايا المتعادلة الأطرية ونسبة الخلايا الغير ناضجة للعدد الكلي للخلايا المتعادلة و الخلايا الليمفاوية في اليوم الأول فقط ، وقد أظهرت أيضًا وجود ترابط ذو دلالة إحصائية بين البريسيبسن مع الهيموجلوبين و الهيماتوكريت و العدد الكلي لخلايا الدم البيضاء و الخلايا الليمفاوية و الخلايا المجزأة ونسبة الخلايا الغير ناضجة للعدد الكلي للخلايا المتعادلة في اليوم الثالث فقط ، وأظهرت أيضًا وجود ترابط ذو دلالة إحصائية بين البريسيبسن مع الهيموجلوبين و الهيماتوكريد و الخلايا المجزأة والخلايا المتعادلة الأطرية و نسبة الخلايا الغير ناضجة للعدد الكلي للخلايا المتعادلة و الخلايا الليمفاوية و عدد الصفائح الدموية في اليوم السابع فقط ، كما أظهرت الدراسة وجود ترابط ذو دلالة إحصائية بين مستوي البريسيبسن مع مستوى بروتين سي التفاعلي في اليوم الأول والثالث و السابع للولادة.