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ORIGINAL ARTICLE

Significance of Plasma Melatonin as a Diagnostic Marker in Full-term with Late Onset Sepsis

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Abstract

Background: When newborn sepsis occurs, the pathogen may trigger an uncontrollable systemic inflammatory response that results in oxidative damage. Melatonin released naturally, which acts as a safe antioxidant and free radical scavenger in newborns. The aim of the work was to evaluate the significance of plasma melatonin level in early diagnosis of late onset sepsis neonatal sepsis. **Methods:** 58 full-term babies were included in a case-control study at Zagazig University's neonatal intensive care unit. Twenty-nine newborns in the patient group had complete clinical and biochemical signs of sepsis. The control group included twenty-nine newborns with no clinical or biochemical signs of sepsis. Melatonin level was measured by ELISA, and a septic work-up was done for all the patients. **Results:** The best cutoff plasma melatonin level in the diagnosis of late onset sepsis was16.2 pg/ml with an area under the curve of 0.97, a sensitivity of 92.6%, specificity of 86.4%, positive predictive value of 90.5 %, negative predictive value of 87% and over all accuracy of 88.6%. **Conclusions:** A significant elevation of endogenous plasma melatonin level was found in late-onset neonatal sepsis, so early identification of late-onset sepsis could considerably help cases by allowing both the prevention of complications and avoiding multiple drug resistance.

Keywords: Neonatal sepsis, Late-onset sepsis, Melatonin, Full-term.

INTRODUCTION

Despite general advance in the neonatal intensive care, sepsis remains a leading cause of death worldwide [1]. Overall, it is estimated to affect 1 in 1000 live newborns [2].

Melatonin is synthetized from the neurotransmitter serotonin and secreted from the pineal gland. Tt is a neuro-hormone that has a wide-ranging regulatory role. [3]

Melatonin is essential for many critical physiological processes, such as the maintenance of circadian rhythms and the regulation of neuroendocrine, neuroimmunology, ocular, and reproductive processes [4].

Melatonin is a broad-spectrum anti-apoptotic, antioxidant, and potent free radical (FRS) scavenge [3].

Pathogen-stimulated infection and systemic inflammatory syndrome lead to a strong immune response that triggers an intracellular redox cascade, which causes mitochondrial, cell, and organ malfunction and ultimately results in neonatal sepsis [5].

The damage that inevitably follows is called oxidative stress (OS), and it is caused by free radicals. It has now been extensively proven that melatonin directly scavenges reactive oxygen species. Melatonin and its metabolites effectively interact with reactive oxygen species (ROS), reactive nitrogen species (RNS), and organic radicals [6]. Late onset sepsis diagnosis requires a fast, sensitive, and specific diagnostic laboratory marker. We postulated that full-term endogenous melatonin level is higher in neonatal sepsis and it can be used as an

early diagnostic marker. We also in need for further research to compare the levels of serum melatonin in late onset full term sepsis before and after receiving empirical antibiotic treatment.

We aimed to assess plasma melatonin's level as a diagnostic marker for late-onset sepsis.

METHODS

This case-control study was conducted on Neonatal Intensive Care Unit (NICU), Zagazig University Hospitals. An informed written consent was taken from the parents. The protocol was approved by the Research Ethical Committee of Zagazig University hospitals (11374/1/2024). This study included 58 full-term neonates whose gestational age (≥37-≤ 42) weeks. The patient group comprised 29 newborns who exhibited all clinical and biochemical laboratory markers of late-onset sepsis (sepsis that occurs after the first 48–72 hours of life) [7]. The diagnosis of sepsis depends on signs and laboratory parameters, including Rodwell's hematological score of ≥3 [8] and 29 matched healthy full-term babies in the control group were enrolled.

We did not enroll full-term babies with hypoxia, neonates with high oxygen requirements on invasive or non-invasive mechanical ventilation, or newborns for mothers with pre-eclampsia or diabetes, as these conditions can raise free radical levels in full-term babies.

All cases were subjected to the following: careful history-taking (prenatal, natal, and postnatal), clinical examination: age in days, determination of gestational age, assessment of anthropometric measurements (weight, length, and head circumference) and clinical evidence of neonatal sepsis as: lethargy, poor Moro and suckling reflexes., temperature instability, respiratory distress: apnea, tachycardia, bradycardia, poor perfusion gastrointestinal manifestations (vomiting diarrhea, abdominal distension, and hepatosplenomegaly) ,colors (jaundice-cyanosis , and pallor), bleeding tendency convulsions-hypotonia. , umbilical sepsis., skin mottling, and scleroderma.

Blood samples were withdrawn from all neonates. **Routine laboratory investigations, including:** 1- Complete blood count (CBC): including hemoglobin (Hb %), hematocrit value, platelet counts, total leukocytic counts (TLC) with differential, immature/total neutrophil ratio (I/T). Method: Two mL of venous blood were taken from each neonate on a 20 uL EDETA solution, and a differential count was done on a Leishman-stained peripheral blood smear. The evaluation was done using a Coulter T660.

2- C - reactive protein (CRP): quantitive CRP measured by latex agglutination test, which is based on an immuno-chemical reaction between CRP and antibodies against CRP bound to latex particles. Positive results will be obtained at concentrations > 6mg/L.

3- Liver and kidney functions. 4- Blood culture: blood culture was obtained on the first suspicion of infection before starting antibiotic treatment. Cases with negative blood cultures were excluded.

Specific laboratory investigation:

The melatonin level in the plasma was measured in both groups. The measurement of plasma melatonin assay protocol adheres to the fundamental idea of competitive ELISA, which states that a biotinylated and a nonbiotinylated antigen compete with one another for a set number of antibody binding sites. The concentration of the sample is inversely correlated with the quantity of biotinylated antigen bound to the antibody. Following a washing process, the free biotinylation is eliminated once the system is in equilibrium. Using p-nitrophenyl phosphate as the substrate and anti-biotin alkaline phosphatase as a marker, the antibody-bound biotinylated antigen is identified. By comparing the enzymatic activity of unknowns with a response curve created using recognized standards, unknowns can be quantified [9].

Statistical Analysis: The Statistical Package of Social Services (SPSS) version 24 was used on a computer to evaluate the data that had been gathered. The data was presented using tables. For continuous quantitative data, the mean ± SD and median (range) were utilized, whereas absolute frequencies (number) and relative frequencies (%) were employed to represent categorical qualitative variables. The following tests are used: performance tests, correlation tests, MW (Mann-Whitney U test), X2 (chi-square test), t (student's T test), and P value: less than 0.05 was significant and less than 0.001 was highly significant.

RESULTS

The results have been summarized, tabulated, statistical analysed, and illustrated in the following tables.

The characteristics of participants were displayed in **(Table 1)**. Regarding the age of presentation, sex, weight, length and mode of delivery, there was no statistically significant difference between the studied groups.

Poor feeding (100% of cases), hypotonia (93%), respiratory distress (72.4%), lethargy (62%), hypothermia (51.7%) and pallor (10.3%) were the most common presentations among the patient group **(Table 2).**

Complete blood count (CBC) and C-reactive protein (CRP) in both groups revealed that there was no significant difference in Hb level, however, there was a significant difference in TLC and a highly significant difference in platelet count, I/T ratio and CRP. **(Table 3)**

Coagulase-negative staphylococci were the most frequent gram-positive organisms. Followed by methicillin-resistant staphylococci (MRSA), Staphylococcus epidermidis, Streptococcus agalactiae, and Streptococcus pneumoniae. However, Klebsiella pneumonia was the most frequent gram-negative organism, followed by Pseudomonas aureginosa and Enterobacter species **(Table 4).**

The melatonin level was highly significantly different in **(Table 5)** between the studied groups, where the median value of melatonin in the patient group was 32.6 pg/mL and in the control group was 9.4 pg/mL.

There was a highly significant positive correlation between melatonin and CRP in the patient group and a significant positive correlation with the control group. However, there was a significant negative correlation between platelet count and melatonin in the patient group and a highly significant negative correlation with the control group **(Table 6).**

The best cutoff point of plasma melatonin in the diagnosis of late-onset sepsis was 16.2 pg/ml with an area under the curve of 0.97, a sensitivity of 92.6%, a specificity of 86.4%, a positive predictive value of 95.5%, a negative predictive value of 87%, and an overall accuracy of 88.6% **(Table 7).**

Table (1): Comparison between studied groups as regards the age of presentation, sex, weight, length, and mode of delivery:

	patient group (n=29)	**Control group** (n=29)	**Test of sig.**	**P**	**Sig.**
Age of presentation (days):			***MW***		
X ± SD	12.4 ± 6.5	10.1 ± 7.6	-1.5	0.15	**NS**
Median	10.0	8.0			
Range	5.0 – 28.0	2.0 – 28.0			
Sex:			X^2		
Males	17 59.0%	18 62%	1.2	0.3	**NS**
Females	12 41.0%	11 38%			
Weight (Kgs):			***t***		
X ± SD	2.9 ± 0.2	3.0 ± 0.5	-0.2	0.8	**NS**
Median	2.9	3.1			
Range	2.7 – 3.3	2.8 – 3.5			
Length (cm)			***t***		
X ± SD	47.0 ± 0.5	46.0 ± 0.6	-0.2	0.8	**NS**
Median	47.0	46.0			
Range	44.0 – 50.0	45.0 – 50.0			
Mode of delivery:			X^2		
Normal vaginal	9 31%	11 38%	0.1	0.8	**NS**
Cesarean section	20 69%	18 62%			

MW: Mann-Whitney U Test ***X^2:*** Chi-square test ***t:*** Student's T test.

Table (2): Clinical presentation of patient group on admission:

Clinical presentation on admission	No.	%
Poor feeding	29	100
Hypotonia	27	93
Respiratory distress	21	72.4
Lethargy	18	62
Hypothermia	15	51.7
Pallor	3	10.3

Table (3): Complete Blood Count (CBC) and C-reactive protein (CRP) of the studied participants

Variable	patient group (n=29)	Control group (n=29)	Test of sig.	P	Sig.
HB (g\dl):					
X ± SD	13.2 ± 3.1	13.8 ± 1.7	***t***		
Median	13.5	14.0	-0.7	0.5	**NS**
Range	10 – 17.0	11.0 – 16.5			
TLC (x10³/ul):					
X ± SD	7.7 ± 3.5	9.9 ± 2.1	***t***	*	
Median	7.2	10.0	-2.5	0.01	**S**
Range	3.0 – 17.0	6.0 – 14.0			
Immature/Total neutrophil			***t***	**	
X ± SD	0.34 ± 0.05	0.15 ± 0.02	15.0	0.000	**HS**
Median	0.33	0.16			
Range	0.27 – 0.45	0.12 – 0.18			
platelet count (x10³/ul):					
X ± SD	128.3 ± 79.4	242.8 ± 78.7	***t***	**	
Median	115.0	210.0	-5.0	0.000	**HS**
Range	46.0 – 375.0	150.0 – 410.0			
CRP (µg/mL):	70.7 ± 31.4	3.2 ± 2.2	***t***	**	**HS**
X ± SD	70.0	3.0	10.1	0.000	
Median	27.0 – 150.0	0.2 – 7.0			
Range					

t: Student's T test *$\mathbf{p} < 0.05$ is statistically significant **$\mathbf{p} \leq 0.001$ is statistically highly significant

Table (4): Blood culture results for patient group

Blood culture results	No.	%
Gram positive organisms (n=16)		
Coagulase negative staphylococci	7	24.1
Methicillin-resistant staphylococci	4	13.8
Staphylococcus epidermidis	3	10.3
Streptococcus agalactiae	1	3.4
Streptococcus pneumonia	1	3.4
Gram negative organisms (n=13)		
Klebsiella pneumonia	9	31.0
Pseudomonas aureginosa	3	10.3
Enterobacter species	1	3.4

Table (5): Melatonin level for study participants

Melatonin level (pg/ml)	patient group (n=29)	Control group (n=29)	*t*	P	Sig.
X ± SD	30.3 ± 10.5	13.1 ± 7.6	6.4	** 0.000	HS
Median	32.6	9.4			
Range	7.0 – 43.8	5.0 – 33.2			

t*:* Student's T test **p ≤0.001 is statistically highly significant

Table (6): Correlation between Melatonin level and variables of studied participants

Variables	patient group (n=29)		Control group (n=29)	
	R	P	R	P
Age	0.3	0.2	0.1	0.8
HB	-0.2	0.3	-0.3	0.2
TLC	0.3	0.1	0.4	0.07
Platelet count	-0.4	0.05*	-0.7	0.000**
CRP	0.6	0.000**	0.5	0.03*

r Pearson correlation coefficient ***p** <0.05 is statistically significant **p ≤0.001 is statistically highly significant

Table (7): Performance of plasma melatonin level in diagnosis of sepsis

	Cutoff	AUC	Sens.	Spec.	PPV	NPV	Accuracy	P
Melatonin	16.2 pg/ml	0.97	92.6%	86.4%	90.5%	87.0%	88.6%	** **<0.001** **HS**

p ≤0.001 is statistically highly significant **PPV positive predictive value **NPV** negative predictive value **AUC** area under curve

DISCUSSION

An indicator of a nation's health is the rate of newborn deaths. Sepsis still to be the world's greatest reason of neonatal morbidity and death. Undeveloped countries have a considerably higher incidence than developed ones, however the frequency varies by country [10].

The most common pathogens in a different neonatal center can be identified through periodic surveys of causative organisms and their sensitivity to antibiotic. As a result, there is less debate about the clinical strategy for treating newborn septicemia [11].

Clinical research supports the role of ROS and RNS in the development of newborn sepsis and its sequelae. Melatonin may be helpful in sepsis and has strong antioxidant and anti-inflammatory properties [12].

Melatonin reduces the production of proinflammatory cytokines and chemokines and the migration of polymorphonuclear leukocytes to the inflammatory regions [3].

Early identification and appropriate treatment of newborn sepsis remain challenging due to its vague signs and symptoms. Numerous studies have been conducted on a range of diagnostic markers, including cell surface markers, C-reactive protein, procalcitonin, cytokines, haematological indices, acute phase reactants, and cytokines. To find a marker with high validity and diagnostic accuracy, more research is necessary. A few of the more recent markers have had encouraging outcomes, which may help identification of newborns with sepsis early on. early identification of sepsis reduces the unnecessary prolonged use of medications and improving the outcome of septic babies [13].

The aim of this work was to assess the diagnostic role of plasma melatonin in late-onset sepsis.

A case control study comprising fifty-eight full-term neonates was studied. 29 full-term newborns showed all clinical and biochemical signs of sepsis; 12 of them were females and 17 of them were males, and the patient group's age at presentation ranged from 5 to 28 days with no significant differences. the same results were reported by Ilke et al. [14], who concluded that in cases where the patient was full term, postnatal or gestational age had no influence on sepsis.

We discovered in this study that there was no statistically significant variance in the frequency of sepsis as regarding the sex. Both Betty and Inderpreet's [15] and De Benedetti et al. [16] studies, which examined 1743 newborns and discovered that the incidence of infection in both genders were identical.

However, the findings of this study were at odds with those of Aggarwalet [17], a study that involved 341 neonates and discovered that male had a greater infection rate (54.3%) than girls (45.7%). Additionally, Gerdes [18] discovered that boys had a much greater frequency of newborn sepsis (male: female ratio, 1.9:1).

Even though the majority of the groups had delivered by caesarean sections, our findings did not show a significant association between the manner of birth and a higher incidence of sepsis. This aligned with the conclusions of Mathai et al. [19]. Conversely, Aguilar and Cecilia [20] found that 45% of newborns with septicemia were delivered vaginally, and 58% of newborns with septicemia were delivered by caesarean section.

There was no appreciable difference in weight across the studied groups. What we found disagreed with Eichenwald [21], whose patient's group had a birth weight of less than 2 kilograms showed symptoms within an hour after delivery, but greater than two-thirds of patients with a bigger birth weight showed symptoms after 4 hours. This is explained the fact, that preterm may be affected by Group B Streptococcus intrauterine, while term babies are often exposed throughout the delivery canal.

The most frequent clinical presentations were Poor feeding (100% of cases), hypotonia (93%), respiratory distress (72.4%), lethargy (62%), hypothermia (51.7%) and pallor (10.3%). Ilke et al. [14] assured our findings, reporting that the most common cause was poor feeding (73%), followed by hypotonia (52%), reduced neonatal reflexes (65%), lethargy (44%), jaundice (33%), and fever (31%).

In cases of neonatal sepsis, leukocytosis refers to an increased number of (WBC) which is a common sign of infection. The (I/T) ratio is a measure used to estimate the risk of infection, a higher ratio suggests more immature neutrophils, raising suspicion for infection. (CRP) is a non-specific tool for inflammation that increases in response to infection or tissue damage Lee et al, [22].

This study demonstrated that hemoglobin levels did not differ significantly; however, the total leucocytic count differed significantly, while platelets, IT ratio, and CRP highly significantly differed.

Hornik et al. [23] observed that both low and high white blood cell counts were linked to neonatal sepsis after studying 204 sick neonates. Neonatal sepsis was found to be associated with greater white blood cell counts in 24 septic babies evaluated by Morag et al. [24]

This study's results, which indicated a significant variance in platelet counts between the two groups, are in line with those of Charoo et al. [25], who concluded that thrombocytopenia is a strong predictor of sepsis. In a study by Lee et al. [22], platelet counts in 24 newborns with blood culture confirmed sepsis and 48 non-septic neonates, matched for gestational age and birth weight, were shown to be considerably lower in the sepsis patients.

This was in agree with those of Makhoul et al. [26], who studied 148 newborns who had suspected sepsis; 111 confirmed as sepsis. They discovered that important predictors of confirmed sepsis were I/T > 0.2 and CRP > 1.0 mg/dl. Furthermore, Bhandari et al. [27] who examined 286 neonates (163 with confirmed or suspected sepsis episodes) and 123 as a control group, found that the sepsis group had lower platelet counts but higher white blood cells. Khair et al. [28], who discovered that the ratios of immature to mature neutrophils (>0.3) and immature to total neutrophils (>0.2) had the best sensitivity and negative predictive values.

De Assis Meireles et al. [29] examined 168 neonates, of whom 33.3% had confirmed neonatal sepsis. They found that the total neutrophil and the immature neutrophil count are useful markers for distinguishing between confirmed and suspected sepsis.

Early identification of newborn sepsis is still challenging, despite recent advancements in NICU. The golden standard for determining a newborn's sepsis is a positive blood culture. we discovered that the patient group had 100% positive blood cultures. Most of the bacteria isolated from blood were gram-positive organisms in 16 cases, were distributed as coagulase-negative staphylococci (24.1%), methicillin-resistant staphylococci (13.8%), staphylococcus epidermidis (10.3%), streptococcus agalactiae (3.4%), streptococcus pneumonia (3.4%). Gram-negative organisms were 13 cases, including klebsiella pneumonia (31.0%), pseudomonas aureginosa (10.3%) and enterobacter species (3.4%). Pathogens isolated during the De Bendetti et al. [16] included pseudomonas aeruginosa (20%), Escherichia coli (10%), and Klebsiella pneumoniae (47.5%).

According to Pandita et al.'s [11] research, gram-negative bacteria (E. Coli, Klebsiella, S. aureus, and Coagulase negative staphylococcus) are the primary causative organisms. The majority of these bacteria are not responding to numerous treatments. This study's concerning finding is the high percentage of bacteria resistant to common antibiotics, which could be attributed to the public's negligent use of these drugs.

By lowering the generation of cytokines and chemokines, also the migration of polymorphonuclear leucocytes to the inflammatory areas, melatonin exhibits potent antioxidant and anti-inflammatory activities [3]. we discovered that, there was a highly significance variance in melatonin levels between the studied groups, with the patient group exhibiting a much greater level than the control group. Melatonin levels in the examined groups highly significantly differed; the median value in the patient group was 32.6 Pg/ml, whereas it was 9.4 Pg/ml in the control group.

Gitto et al. [30] were paralleled to our results, who examined the clinical status of 110 septic ventilated babies before and after melatonin administration, as well as pro-inflammatory cytokines (IL6, IL-8, and TNF-α). The concentration of TNF-α, IL-6, and IL-8 in the two groups were assessed, and the results showed that melatonin treatment reduced inflammation.

Mundigler et al. [31] assessed the melatonin level in severely ill newborn to explain whether melatonin and the severity of septic shock are associated. The results were significantly worse in septic patients.

There was a highly significant positive correlation between melatonin and CRP in patient group and significant positive correlation with control group. However, there was a significant negative correlation between platelet count and melatonin in the patient group and a highly significant negative correlation with the control group.

Evidence was presented by this study for the efficacy of melatonin level as a marker of sepsis. Melatonin accuracy was 88.6%, sensitivity and specificity were 92.6% and 86.4%, positive and negative predictive values were 90.5% and 87%, likelihood ratios were 6.8, 0.09, and positive and negative predictive values were 90.5% and 87% at the cutoff point of 16.2 pg/ml. These differences in prenatal characteristics, inclusion criteria, ICU environment, developmental care, neonatal comorbidities, and various drugs that may interact with endogenous melatonin release and metabolism could all be contributing factors to the different data among studies. Consequently, it is advised to conduct more researches with a numerous cases, extended follow-up, and more serial melatonin testing.

CONCLUSION

Plasma melatonin played a significant role in the early diagnosis of late- onset sepsis.While waiting for the findings of a blood culture, the diagnostic value of both single and combination tests was important in the early identification of clinically suspected neonatal sepsis. Nevertheless, achieving 100.0% sensitivity was beyond the reach of any combination test.

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