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ORIGINAL ARTICLE

Endocan as a Novel Marker of Neonatal Sepsis

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ABSTRACT

Background: Endocan is a specific molecule of human endothelial cells and it is a promising biomarker to predict sepsis and mortality. Serum levels of endocan increase in patients presenting with sepsis. This study aimed to evaluate the serum endocan levels in neonates suffering from sepsis to assess its value in early diagnosis.

Methods: This cross-sectional study was carried out at Neonatal Intensive Care Unit (NICU), Pediatric Department, Zagazig General Hospital during the period from January to July 2018 with a total number of 24 neonates diagnosed with early-onset sepsis. Serum Endocan was measured before treatment and 3 days after treatment.

Results: Serum Endocan level was significantly higher before treatment than after treatment. There was a positive significant correlation between Endocan level and sepsis, P-value < 0.05, and r-value=+0.33.

Conclusions: Serum endocan can be used for the diagnosis of early-onset sepsis, serum endocan is a good diagnostic measure of neonatal sepsis.

Keywords Endocan, Marker, Sepsis.
Conflict of interest: No
Financial disclosure: No

INTRODUCTION

Neonatal sepsis is a type of neonatal infection that refers to the presence of bacterial bloodstream infection (BSI) in a newborn baby (such as meningitis, pneumonia, pyelonephritis, or gastroenteritis) in the setting of fever. According to Physicians and the Society of Critical Care Medicine, there are different levels of sepsis **[1].**

Neonatal sepsis is defined as bacteremia accompanied by hemodynamic compromise and systemic signs of infection **[2].**Endocan is an endothelial cell-specific molecule that is expressed by endothelial cells in the lung and kidney. Increased concentrations were described in patients with sepsis and septic shock compared to healthy individuals **[3].** In patients with steps, the is, the endocan blood level is related to the severity of illness and may represent a novel endothelial cell dysfunction **[4].** Endocan's blood levels have been found elevated in septic patients with increasing severity of illness as well as in immunocompromised patients with complicating bacterial infections. This underlines a possible future role in the differential diagnosis of the systemic inflammatory response syndrome and a predictive value in terms of clinical outcome **[5].** Endocan is implicated in the recruitment of circulating lymphocytes to inflammatory sites and leucocyte adhesion and activation as it binds directly to LFA-1 on human blood lymphocytes and monocytes also inhibit leukocyte-endothelial cell adhesion and reduce the excessive leukocyte recruitment into the lung**[6].**

Methods:

- This cross-sectional study was conducted in the Neonatal Intensive Care Unit (NICU) at Zagazig General Hospital from January 2018 to July 2018. A total number of 24 neonates were diagnwithed with early-onset sepsis before and 3 days after treatment. In this study (The preterm and full-term neonates were admitted to NICU after birth with early-onset sepsis is included), however; Infant of a diabetic mother, the Infant with congenital anomalies, the Infant with congenital heart disease, the Infant of addicted

mothers are excluded). All neonates enrolled in this study were subjected to:

- **Complete history including {**Obstetric history, Prenatal history, natal history, post-natal history, Present history which includes symptoms of sepsis, history of antibiotics given (type, dose, and duration)**}**.
- **Full clinical examination including**:

Vital signs (temperature, respiratory rate, heart rate), General appearance: activity, edema, pallor, cyanosis, plethora, weight, length, head circumference, and Complete clinical examination to detect clinical signs of sepsis**}.**

General signs: Temperature instability, poor suckling and not doing well.

Respiratory signs: Intercostal retractions, tachypnea or grunting, cyanosis, apnea, increased oxygen requirement.

Circulatory signs: Weak pulses, delayed capillary refill, hypotension, tachycardia, or shock.

GIT signs: Abdominal distention, diarrhea, bloody stool, feeding intolerance, hepatomegaly, or jaundice. **Neurological signs:** Irritability, hypotonia, lethargy, and convulsions.

Metabolic signs: Hypoglycemia or hyperglycemia.

Hematological signs: Petechiaendocae, bleeding, or disseminated intravascular coagulation.

- **Laboratory procedures including:**

1-Routine investigations (Complete blood count**,** blood urea and serum creatinine**,** C-reactive protein**)**

2 - Blood culture and sensitivity:

After cleaning of the puncture site with 70% alcohol and 1% tincture iodine about 1ml of blood was obtained to broth bottle using neonatal bottles and subculture on a blood agar plate. When a blood culture was positive within 72 hours, it was considered true bacteremia. Aerobic and anaerobic cultures on blood agar plates at 10% CO2 and on MacConkey agar were done. Isolated colonies were identified by colony morphology, gram smears, biochemical and enzymatic reactions. If no growth was obtained, the bottles were incubated for up to 10 days with subculture every other day on solid media. If no growth occurred after 10 days of incubation, blood culture was considered negative.

3-Specific investigations:

Serum level of Endocan by ELISA (ESM-1 ELISA Kit). Done before treatment and 3 days after treatment.

- Ethi**cal approval**

All procedures performed in this study were by the ethical standards of the Institutional Review Board (IRB) and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

- **Statistical analysis**

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), Version 23. The numeric variables as mean ± SD, the categorical variables as percentage were expressed. The groups were compared using the chi square-test. Stasquare test p <0.05 was accepted.

RESULTS:

- There was a positive significant correlation between Endocan level and sepsis, indicating that when sepsis occurs there was an increase in the mean level of endocan also, P-value < 0.05, and r-value=+0.33 was presented in table 1.
- There was **a** significant increase in hemoglobin (Hb) levels and platelets count (PLTs) among cases of neonatal sepsis after treatment, a significant decrease in the total leucocytic count (TLC) and I/T ratio among cases after treatment was presented in table 2.
- There was a significant difference between Endocan levels before and after treatment, there is a decrease in the mean level of endocan after treatment compared to its level before treatment, P-value <0.05 presented in Table 3.
- There was a significant positive correlation between Endocan level before and after treatment and TLC that indicates when there was an increase in TLC count there was also an increase in the mean value of endocan level before and after treatment, P-value < 0.05, and r-value=+0.41 presented in table 4.
- There was a positive correlation between endocan level before, after treatment, and TLC was presented in figure 1.
- There was **a** positive correlation between endocan and CRP before treatment was presented in figure 2.
- There was **a** positive correlation between endocan level before and after treatment and results of blood culture in figure 3.

Table (1): Correlation between Endocan level before and after treatment and Onset of sepsis:

Onset of sepsis	Serum level 0f Endocan		Pearson correlation r - value	P-value
	Endocan before treatment	Endocan after treatment		
Early	941.548± 387.456	623.859± 221.873	+0.33	<0.002

Onset of sepsis	Serum level 0f Endocan		Pearson correlation r -value	P-value
	Endocan before treatment	Endocan after treatment		
Late	982.893± 327.459	645.768± 287.8038		

Table (2): Complete blood count in the studied groups:

	Cases before TTT	Cases after TTT	Test of sig	P
HB (g/dl)				
Min. – Max. **Mean ± SD.**	9.40– 23.0 14.004± 3.8044	12.80 – 17.20 15.08 ± 1.41	**t= 10.01***	<0.001*
PLTs (x 10^3/µL)				
Min. – Max. **Mean ± SD.**	38.0 – 298.0 111.25± 46.954	190.0 – 372.80 290.59 ± 56.13	**t=13.532***	<0.001*
TLC (x 10^3/µL)				
Min. – Max. **Mean ± SD.**	3.20– 33.0 17.779± 6.975	5.00 – 11.2 7.24 ± 2.24	**t= 5.005***	<0.001*
I/T ratio				
Min. – Max. **Mean ± SD.**	**0.06 – 0.39** **0.271± 0.8739**	**0.05 – 0.15** **0.14 ± 0.01**	t=10.818*	<0.001*

Table (3): Endocan level before and after treatment

Endocan	Serum Endocan level(g/dl)		Chi-square	P-value
	Endocan before treatment	Endocan after treatment		
Serum Level of Endocan	923.9± 584.8	689.39± 342.7069	3.52	<0.02

Table (4): Correlation between Endocan level before and after treatment and total leucocytic count (TLC)

Total leucocytic count	Serum level 0f Endocan		Pearson correlation r -value	P-value
	Endocan before treatment	Endocan after treatment		
Less than (5) (x 10^3/µL)	923.354± 411.567	618.872± 201.758	+0.41	<0.001
More than (5) (x 10^3/µL)	978.424± 377.631	661.752± 281.837		

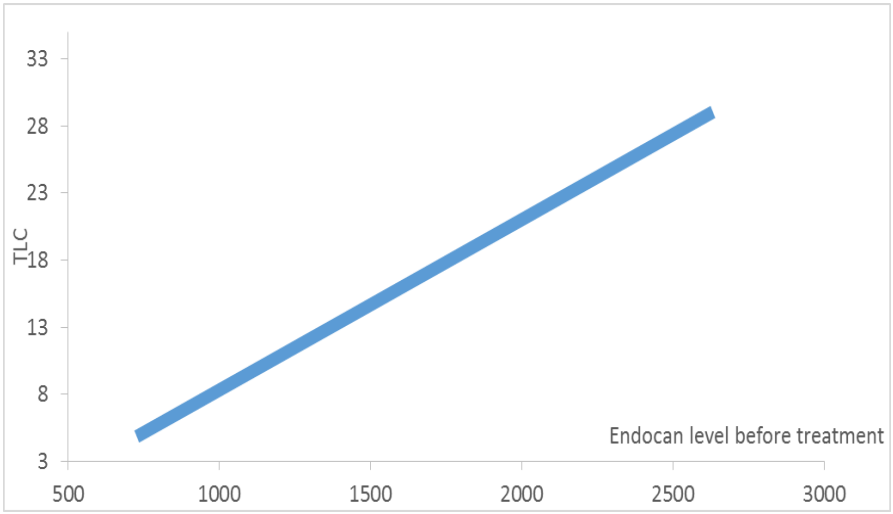

Figure 1: correlation between endocan level before and after treatment and TLC

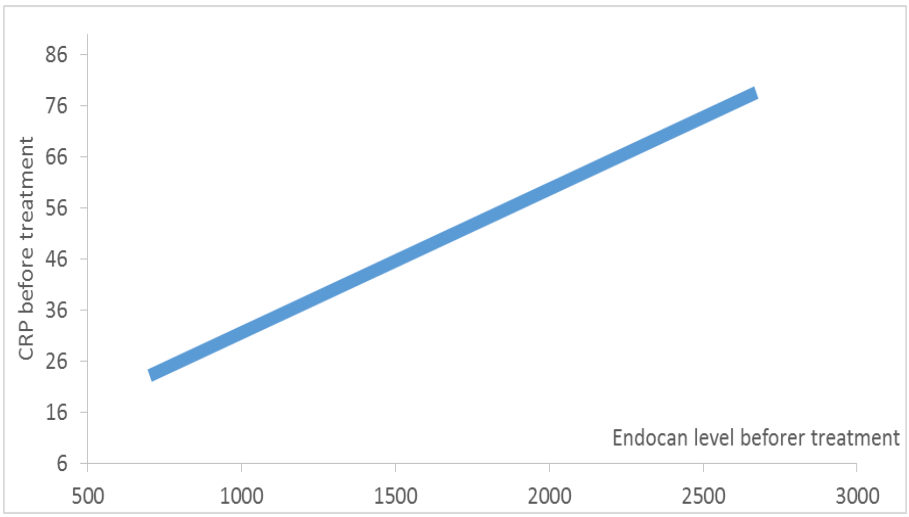

Figure 2: correlation between endocan and CRP before and after treatment:

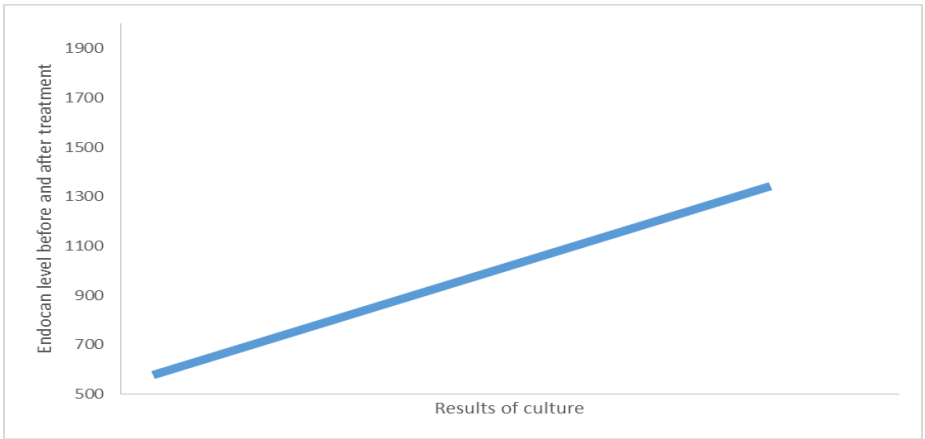

Figure 3: correlation between endocan level before and after treatment and results of blood culture

DISCUSSION

Endocan is a newly recognized biomarker of sepsis. Endocan is a 50-KD dermatan sulfate proteoglycan that can be detected in human blood and is expressed on the surface of endothelial cells of the lungs and kidneys **[7].** A few studies have shown that endocan can be a good marker of endothelial dysfunction and multiorgan failure in sepsis, and it can be accepted as a good marker of survival prognosis in sepsis**[8].** The serum endocan level has also been shown to be related to acute disease other than sepsis,including acute lung injury and acute respiratory distress**[9]**. Serum Endocan concentration may be a useful adjunct test, in addition to blood culture and other markers of infection **[10].**In this study, Fever, multiple births, and PROM are not common risk factors in studied cases as PROM affects only 9 out of 24

cases (37.5%). It disagreed with the study with **Amela et al., [11]** who worked on **340** neonates and found that PROM was the main risk factor in the septic group (70.1%) while the study of **St Game et al., [12]**, showed no statistical significance was found between the sepsis group and control group in terms of PROM. Umbilical catheterization for longer than 5 days, MV for longer than five days, NEC, a birth weight of 2 500 g and lower, use of the nasogastric tube, total parenteral nutrition (TPN), and being referred from another hospital were found to be correlated with neonatal sepsis. In the current study, we found that there was no significant correlation between sepsis and mode of delivery. This was in agreement with **Mustafa et al., [13]** where they found no relation between mode of delivery and sepsis nor neonatal outcome. On the other hand, this was in disagreement with **Aguilar [14]** who studied a total of **3870** neonates, **103** neonates (**68** preterm and **35** full-term) with confirmed sepsis, the authors observed that more than half of the neonates who developed septicemia **58** (56%) were delivered via cesarean section, while **45** (44%) were delivered by vaginal delivery. While in the study of **Stoll,** who studied on a total of **7861** neonates, **147** with early-onset sepsis, he found that babies born by vaginal delivery were more likely to have early-onset sepsis than those delivered by cesarean section. This may be attributed to the fact that those delivered vaginally may be more likely to be contaminated with vaginal flora during labor and delivery **[15].** In this study, results showed a significant decrease in hemoglobin (Hb) levels among groups before treatment compared to groups after treatment and this came in agreement with the study of **Yapakç et al., [16]** which was conducted on **21** neonates (**15** preterm and **6** full-term) with confirmed sepsis and **33** neonates (**17** preterm and **16** full-term) as the control group, the authors found that hemoglobin (Hb) levels were lower in a septic group than in control group. As inflammatory reactions cause a decrease in hemoglobin level this is obvious in anemia of chronic diseases. In the current study, results showed that the platelet count was significantly lower in a group before treatment than group after treatment. This came in agreement with the study of **Manocha V et al., [17]** which was conducted on **150** neonates (from birth to 3 days old) clinically suspected sepsis. (**21** neonates (14%) had blood culture-proven sepsis). The authors found that the platelet count was significantly lower in cases of sepsis than among control cases. In this study results showed that total leukocytes (TLC) was significantly higher in a group before treatment than group after treatment and this came in agreement with the study of **Mohamed and Saeed, [18]** which was conducted on **62** neonates (**27** preterm and **35** full-term) with culture-proven sepsis and **35** controls, the authors found significantly higher TLC in a septic group than in control group.In the current study, results showed that there is a significant correlation between endocan with platelets count and total leukocytic count in studied cases. This came in agreement with the study of **Pauly et al., [19]** which was conducted on **21** neonates (**15** preterm and **6** full-term) with confirmed sepsis and **33** neonates (**17** preterm and **16** full-term) as the control group, the authors found that platelets levels were lower in a septic group than in control group. As inflammatory reactions cause a decrease in platelets level. In the current study, results showed that the platelet count was significantly lower in a group before treatment than group after treatment. In the current study, results showed that Endocan levels were significantly higher in a group before treatment than in the group after treatment. This came in agreement with the study **[20]** which was conducted on **210** patients (**150** patients with sepsis and **60** as a control group). The authors found that the serum endocan level was higher in patients with sepsis (0.57 ng/ml - 0.76 ng/ml) compared to the control group (0.24 ng/ml - 0.30 ng/ml).

CONCLUSIONS:

Serum endocan can be used for early diagnosis of neonatal sepsis, serum endocan is a good diagnostic measure of neonatal sepsis

Limitation of the study: Relatively small sample size due to high cost concerning the measurement of endocan.

Recommendation of the study: Large multicenter trials are needed to evaluate if endocan use can improve diagnosis and follow-up of infection to reduce unnecessary antibiotic administration.

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