PLASMA ANTITHROMBIN AND PROTEIN C LEVELS IN EARLY RECOGNITION OF LATE-ONSET SEPSIS IN NEWBORN INFANTS ADMITTED TO NEONATAL INTENSIVE CARE UNIT AT BENHA SPECIALIZED CHILDREN HOSPITAL

By

Khaled Mahmoud Zayed (MD)*, Amr Hemeda Mustafa (MD)*, Ahmed Abd El-Moez Ali Saad (MD), Mostafa Abd El-Azim Mostafa (MD)*** and Ahmed Amin Hamed Hamed (MBBCh)***

Pediatric* and Clinical Pathology** departments Faculty of Medicine, Al-Azhar University (Cairo), Pediatric departments Faculty of Medicine Benha University***

ABSTRACT

Background: *Late-onset infections present after delivery, or beyond 3 to 7 days of age, and are attributed to organisms acquired from interaction with the hospital environment or the community. 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, can lead to delays and errors in diagnosis. 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. Antithrombin and protein C (PC) play a major role in the regulation of coagulation, shifting thrombin from procoagulant to anticoagulant.

Objectives: *The aim of this study was to evaluate the Plasma Antithrombin and protein C levels in early recognition of late-onset sepsis in newborns. The study is also designed to determine the possible relationship between the types of bacteria and the values of plasma Antithrombin and Protein C levels.*

Subjects and Methods: *This is a hospital based prospective study conducted on 60 neonates with suspected LOS & 30 neonates as control at the neonatal intensive care unit (NICU) of Benha children hospital during the period from October 2019 to February 2020. They were selected by simple random method. The studied neonates were classified into three groups: 1-Control group consists of 30 healthy neonates. 2-sepsis non confirmed group consists of 30 neonates (-ve blood culture). 3-sepsis confirmed group consists of 30 neonates (+ve blood culture).*

All groups were subjected to complete history taking, clinical examination, Serum Plasma Antithrombin and protein C levels were measured.

Results: *The results of this study showed marked decrease in the level of the physiologic inhibition system of coagulation including antithrombin, and protein C in 100% of cases, compared to the control group ($p < .001$). Also we found mortality incidence was 13.3% in Suspected Sepsis, 36.7% in Confirmed Sepsis. Antithrombin and protein C levels are decreased in late onset sepsis, Anti-thrombin in Suspected Sepsis was (54.9 ± 10.7) % & in Confirmed Sepsis was (35.7 ± 9.05) % while Protein C in Suspected Sepsis was (41.2 ± 8.5) % & in Confirmed Sepsis was (15.3 ± 6.4) % with highly significant difference between studied groups.*

Conclusion: *Anti-thrombin and Protein C have high predictive value in diagnosis of LOS as their level were significantly lower in neonates with sepsis, either confirmed or suspected.*

Keywords: *Antithrombin, Protein C, Neonate, Sepsis.*

INTRODUCTION

The term neonatal sepsis is used to designate a systemic condition of bacterial, viral, or fungal (yeast) origin that is associated with hemodynamic changes and other clinical manifestations and results in substantial morbidity and mortality **(Wynn JL et al., 2014)**.

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., 2016)**.

Neonatal sepsis includes septicemia, pneumonia, meningitis, osteomyelitis, arthritis and urinary tract infections, and does not yet have a consensus case definition, especially for Low- and Middle- Income Countries (LMICs) **(Schlapbach LJ, Kissoon N, 2018)**.

Neonatal sepsis has been classified as either early-onset or late-onset depending on the age of onset and timing of the sepsis episode. Late-onset infections present after delivery, or beyond 3 to 7 days of age, and are attributed to organisms acquired from interaction with the hospital environment or the community **(Annane et al., 2016)**.

Three out of every ten deaths due to neonatal sepsis are thought to be caused by resistant pathogens **(Laxminarayan R, et al., 2016)**.

Antithrombin and protein C (PC) play a major role in the regulation of coagulation, shifting thrombin from procoagulant to anticoagulant **(Harmon, S. et al., 2014)**.

AT and PC plasma levels decrease in sepsis and, when low,

predict high mortality **(Macias WL, Nelson DR, 2004)**.

Antithrombin is a serine protease inhibitor that regulates the intrinsic, extrinsic and common clotting pathways through inactivation of multiple coagulation factors, including factor Xa and thrombin. AT may also have other roles such as reducing platelet adhesion to fibrinogen **(Brady S. et al., 2017)**.

Antithrombin (AT) and protein C (PC) levels decrease in sepsis at birth, (PC) and (AT) are present at approximately 20–60% of adult levels **(Fernández et al., 2016)**. Several studies have reported that plasma levels of antithrombin and protein C are significantly lower in patients with poor prognosis.

Aims of the Work

The aim of this study is to evaluate Plasma Antithrombin and protein C levels in early recognition of late-onset sepsis in newborns. The study is also designed to determine the possible relationship between the types of bacteria and the levels of plasma Antithrombin and Protein C.

Ethical Considerations:

1. Approval of ethical committee in the university was obtained before the study.
2. Full informed consent was taken from parents or care giver.
3. Privacy of participants and confidentiality of the data were maintained.
4. The care givers have the right to withdraw from the study at any time.
5. The authors declared that there is no conflict of interest or any financial support regarding the study or publication.

PATIENTS AND METHODS

Patients: This is a hospital based prospective study conducted on 90 neonates at the neonatal intensive care unit (NICU) of Benha children hospital during the period from October 2019 to February 2020 were the material of this study they were selected by simple random method.

Inclusion criteria were:

1. Healthy newborn as control group.
2. Full term or pre-term.
3. Clinical evidence of late onset sepsis.
4. Post natal age 3 days up to 30 days.
5. The sepsis confirmed group was defined as having positive blood culture associated with clinical signs of sepsis during

the neonatal period (3-30 days after birth).

Exclusion criteria were:

1. Infants with major congenital anomalies or malformations.
2. Evidence of HIE or Intracranial hemorrhage.
3. Newborn with evidence of IEM.
4. Evidence of congenital heart disease.

Methods:

Our studied cases were 90 neonates FT or PT aged 3-30 days they are classified into 3 groups:

Group I: control group consists of 30 healthy neonates.

Group II: Late onset sepsis with – ve blood culture consists of 30 neonates (not confirmed group).

Group III: Late onset sepsis confirmed group consists of 30 neonates by +ve blood culture.

All neonates included in the study subjected to the following:

- Full history taking antenatal, natal & post natal laying stress on history suggestive of Late onset sepsis.

Complete clinical examination laying stress on signs of Late onset sepsis.

- **Laboratory evaluation including:**
  - CBC with differential leucocytic count, (I/T ratio).
  - Chemistry (Na, k, Ca, Kidney & liver function tests) when needed.
  - Quantitative CRP was measured normal range less 6 mg/dl.
  - Sepsis Screen (Blood culture, Urine culture, C.S.F culture when needed).
  - Plasma Antithrombin and protein C levels, obtained as a single measurement.

Assay of Antithrombin:

Measurement of plasma Antithrombin antigen was done using Antigenic assay of antithrombin concentration by the immunoturbidimetric method with normal level range from 60-120%.

Assay of Protein C:

Enzyme-linked immunosorbent assay (ELISA) for the quantitative determination of Protein C Antigen in citrated human plasma with normal level range from 72-160 %.

Statistical Analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 24. Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Chi-square test: was used when comparing between non-parametric data. A one-way analysis of variance (ANOVA): when comparing between more than two means. ROC curve (Receiver Operating Characteristic Curve): was used to detect cutoff value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

RESULTS

Table (1): Demographic data among studied groups

		Studied groups						P-value
		No sepsis (N = 30)		Suspected Sepsis (N = 30)		Confirmed Sepsis (N = 30)		
Sex	Male	20	66.7%	21	70%	19	63.3%	0.861 NS
	Female	10	33.3%	9	30%	11	36.7%	
Post natal Age (days)	Mean	6.9		20.4		18.9		< **0.001 HS**
	±SD	4.8		14.8		8.7		
Gestational age (weeks)	Mean	37.7		35.5		34.6		< **0.001 HS**
	±SD	1.1		3.1		3.7		
Weight (kg)	Mean	2.95		2.3		2.19		< **0.001 HS**
	±SD	0.4		0.6		0.7		

NS: p-value > 0.05 is considered non-significant.
HS: p-value < 0.001 is considered highly significant.

This table shows highly statistical significant difference (p-value < 0.001) between studied groups as regard age, gestational age & weight.

Table (2): Comparison between studied groups as regard clinical presentation

	Studied groups						P-value
	No sepsis (N = 30)		Suspected Sepsis (N = 30)		Confirmed Sepsis (N = 30)		
Jaundice	30	100%	3	10%	0	0%	**< 0.001 HS**
Convulsion	0	0%	3	10%	7	23.3%	**0.016 S**
Respiratory distress	0	0%	26	86.7%	26	86.7%	**< 0.001 HS**
Apnea	0	0%	9	30%	12	40%	**0.001 S**
Cyanosis	0	0%	6	20%	4	13.3%	**0.043 S**
Bulging ant. Fontanelle	0	0%	0	0%	6	20%	**0.002 S**
hypoactivity	0	0%	12	40%	20	66.7%	**< 0.001 HS**
Sclerema	0	0%	1	3.3%	5	16.7%	**0.024 S**
Shock	0	0%	1	3.3%	4	13.3%	0.064 NS

This table shows Statistical significant difference between studied groups as regard convulsion, apnea, cyanosis, bulging ant. F, sclerema and shock.

Highly statistical significant difference between studied groups as regard jaundice, respiratory distress, hypoactivity.

Table (3): Comparison between studied groups as regard CBC

		Studied groups			P-value
		No sepsis (N = 30)	Suspected Sepsis (N = 30)	Confirmed Sepsis (N = 30)	
WBCs (x10³/ul)	**Mean**	12.9	16.6	19.9	**0.003 S**
	±SD	3.3	5.6	11.5	
Neutrophil (%)	**Mean**	59.1	71.7	72.1	**< 0.001 HS**
	±SD	3.7	4.05	4.01	
Segmented (%)	**Mean**	53.03	56.4	58.8	**0.017 S**
	±SD	5.3	7.9	9.4	
Staff (%)	**Mean**	4.9	9.6	13.8	**< 0.001 HS**
	±SD	1.5	1.8	2.6	
I/T ratio	**Mean**	0.09	0.17	0.23	**< 0.001 HS**
	±SD	0.02	0.02	0.04	
Hb (g/dl)	**Mean**	14.9	12.5	10.9	**< 0.001 HS**
	±SD	2.6	2.8	2.4	
HCT (%)	**Mean**	43.8	36.03	31.1	**< 0.001 HS**
	±SD	8.2	9.6	6.7	

PLT (x10³/ul)	**Mean**	360.9	365.4	293.1	0.147 NS
	±SD	114.4	165.9	186.2	

This table shows Statistically significant difference (p-value < 0.05) between studied groups as regard WBCs & segmented neutrophil. Highly statistical significant difference (p-value < 0.001) between studied groups as regard neutrophil, staff, I/T ratio, Hb & HCT.

Table (4): Comparison between studied groups as regard quantitative CRP value.

		Studied groups			P-value
		No sepsis (N = 30)	**Suspected Sepsis (N = 30)**	**Confirmed Sepsis (N = 30)**	
CRP mg/dl	**Mean**	0.4	37.7	70.5	**< 0.001 HS**
	±SD	1.5	21.3	42.5	

This table shows highly statistical significant difference (p-value < 0.001) between studied groups as regard CRP

Table (5): Blood culture results in patients with confirmed sepsis.

		Confirmed sepsis (N = 30)	
Blood culture results	**Klebsiella**	20	66.7%
	Staph aureus	7	23.3%
	Staph aureus (MRSA)	2	6.7%
	Pseudomonas	1	3.3%

This table shows Klebsiella was in 20 patients (66.7%), staph aureus in 7 patients (23.3%), staph aureus (MRSA) in 2 patients (6.7%) & pseudomonas in 1 patient (3.3%).

Table (6): Comparison between studied groups as regard anti-thrombin and protein C

		Studied groups			P-value
		No sepsis (N = 30)	**Suspected Sepsis (N = 30)**	**Confirmed Sepsis (N = 30)**	
Anti-thrombin%	**Mean**	92.9	54.9	35.7	**< 0.001 HS**
	±SD	14.04	10.7	9.05	
Protein C%	**Mean**	66.7	41.2	15.3	**< 0.001 HS**
	±SD	12.6	8.5	6.4	

This table shows highly statistical significant difference (p-value < 0.001) between studied groups as regard anti-thrombin & Protein C.

Table (7): Correlation of Anti-thrombin & protein C levels and type of organism in patients with confirmed sepsis

	Klebsiella (n = 20)	**MRSA (n = 2)**	**Staph aureus (n = 7)**	**Pseudomonas (n = 1)**
Anti-Thrombin %	34.3	39	40	28
	± 9.5	± 4.2	± 8.1	----
Protein C %	14.2	22.5	16	18
	± 6.8	± 2.1	± 5	----

This table shows that Antithrombin decreased more with pseudomonas & klebsiella while protein C decreased more with staph aureus& klebsiella.

Table (8): ROC Curve, Sensitivity, and Specificity of Anti-thrombin in diagnosis of sepsis

Cut off	**Area under the curve**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**p-value**
< 42.5	**0.91**	**76.7 %**	**90 %**	**88.5 %**	**79.4 %**	**< 0.001**

PPV: positive predictive value, AUC: Area under curve
NPV: negative predictive value.

Using roc curve, it was shown that Anti-thrombin can be used to discriminate between patients with confirmed sepsis and patients with suspected sepsis at a cutoff level of < 42.5, with 76.7% sensitivity, 90% specificity, 88.5% PPV and 79.4% NPV (AUC = 0.91, p-value < 0.001).

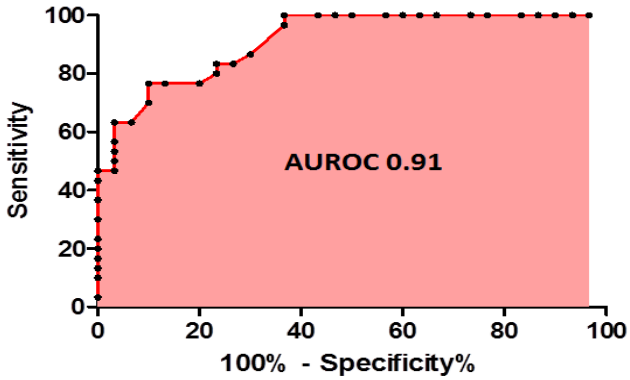

Figure (1): ROC curve between patients with confirmed sepsis and patients with suspected sepsis as regard Anti-thrombin

Table (9): ROC Curve, Sensitivity, and Specificity of protein C in diagnosis of sepsis

Cut off	Area under the curve	Sensitivity	Specificity	PPV	NPV	p-value
< 28	**0.99**	**100 %**	**96.7 %**	**96.8 %**	**100 %**	**< 0.001**

PPV: positive predictive value, AUC: Area under curve
NPV: negative predictive value.

Using roc curve, it was shown that protein C can be used to discriminate between patients with confirmed sepsis and patients with suspected sepsis at a cutoff level of < 28, with 100% sensitivity, 96.7% specificity, 96.8% PPV and 100% NPV (AUC = 0.99, p-value < 0.001).

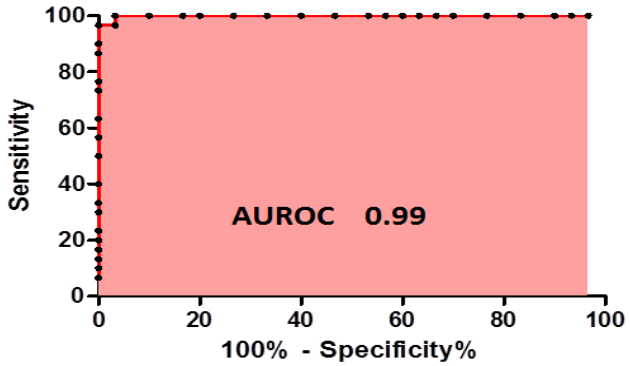

Figure (1): ROC curve between patients with confirmed sepsis and patients with suspected sepsis as regard protein C

Table (10):Comparison between studied groups as regard outcome

		Studied groups						P-value
		No sepsis (N = 30)		Suspected Sepsis (N = 30)		Confirmed Sepsis (N = 30)		
Outcome	Died	0	0%	4	13.3%	11	36.7%	0.001 S
	Still alive	30	100%	26	86.7%	19	63.3%	

S: p-value < 0.05 is considered significant.

This table shows statistically significant difference (p-value < 0.05) between studied groups as regard outcome.

DISCUSSION

The global epidemiological burden of sepsis is difficult to ascertain. It is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths. The burden of sepsis is most likely highest in low- and middle-income countries, it is estimated that 3 million newborns and 1.2 million children suffer from sepsis globally every year **Fleischmann-Struzek C. et al., (2018)**.

Although reported incidence rates of neonatal sepsis from low-resource countries are generally higher, cases are likely under ascertained owing to many factors, including lack of access to care, poor quality care, and lack of adequate laboratory services. In one review of community-based studies from low- and middle-income countries, incidence rates ranged from 49 to 170 cases per 1,000 live births across 11 studies **Lawn, J. E. et al. (2017)**.

In this study there was Male predominance with a male to female ratio of 2:1. **Abosalem, et al. (2009)** found that there was Male predominance with a male to female ratio of 1.5 was found in his study.

In this study, respiratory distress have founded in 86.7%% of cases in confirmed & suspected sepsis, apnea was 30% in suspected & 40% in confirmed cases, hypoactivity was 40% in suspected & 66.7% in confirmed cases, convulsions 10% in suspected & 30% in confirmed cases, and sclerema was present in 3.3% in suspected & 16% in confirmed cases. **Regelmann w. (2017)** had stated that the signs and symptoms of the sepsis in the newborn are nonspecific. On clinical evaluation of our septic patients, respiratory distress, vomiting , hypoactivity and poor reflexes were the commonest

clinical presentations (86.7%, 60%, 66%, 53%, respectively) agreeing with **ahmed et al. (2000)** who found poor Moro and suckling reflexes in 98% and 94.9% respectively, and also agreeing with **Abosalem, et al. (2009)** who described as clinical evaluation of patients, poor Moro , respiratory distress and poor suckling reflex were the commonest clinical presentations (100%,56.6,50% respectively).

In our study, a wide range of total leucocytic count was present (with mean 16.6 $x10^3$/ul In suspected & 19.9 $x10^3$/ul in confirmed cases) agreeing with **Abosalem, et al. (2009)** found that there is wide range of total leucocytic count was present (ranging between 3.5 and 26.5 x 10 / mm, 20 % had leukocytosis and 13.3 % were leukopenia) which was also documented in the study done by **El- Maraghy et al. (1995)**.

In this study, the septic cases which had I / T ratio was highly significant more than 0.2 represented this is attributed to the release of neutrophils from bone marrow in response to infection, with increasing number of immature cells entering the blood stream and producing a differential cell count with a shift to the left , this agrees with **Abosalem, et al. (2009)** who found that I / T ratio of more than 0.2 represented 50 %, & also with **Ahmed et al. (2000)** who found I / T ratio more 0.2 in 62.7 % of cases of neonatal sepsis.

In our Studied cases had a positive CRP (99%). this agrees with **Abosalem, et al. (2009), Ahmed et al. (2000)** who found that CRP was +ve in 100% of cases of neonatal sepsis.

Hisamuddin, et al. (2015) stated that the sensitivity and specificity of CRP in diagnosis of acute neonatal sepsis was 76.92% and 53.49% respectively while it had a positive predictive value of 80% and negative predictive value of 48.94%. Over all the diagnostic accuracy of CRP in diagnosis of neonatal sepsis was 70.07%.

Blood culture is the gold standard for the diagnosis of septicemia and should be performed in all cases of suspected sepsis prior to starting antibiotics. A positive blood culture with sensitivity of the isolated organism is the best guide to antimicrobial therapy **Kayange et al. (2010)**.

In the present study, As regards the type of bacteria isolated from blood cultures gram-negative bacteria accounted for the majority of the culture growth, Klebsiella was isolated in 66.7%, on the other hand staph aureus was found

in 23.3%, (MRSA) was found in 6.7%, Pseudomonas was found in 3.3%. The predominance of gram negative bacteria in this study was agree with previous study done in Egypt by **Ahmed et al. (2000)** & **Mohsen et al. (2017)** they found that gram negative bacteria accounted for the majority of the culture growths. Also at a NICU of Beni-Suef University Hospital, the most common organism identified was K. pneumonia **Fahmey S. (2013)**.

On the contrary, in study by **Abosalem, et al. (2009)** gram-positive bacteria accounted for the majority of the culture growth, staph was isolated in 50%, and on the other hand klebsiella was found in 26.7% Enterobacter in 16.7% and E coli on 6.7%. At the study by **El Beshlawy et al. (2010)** showed that the most prevalent organism in the blood culture studies was Staphylococcus aureus. Also a study by **Anwer et al. (2000)** conducted in Karachi; gram positive organisms were the main cause of neonatal sepsis. Also at Ain Shams University, Staphylococcus aureus was the most common organism isolated in neonates with early and late onset sepsis **Draz et al. (2013)**.

In our study we found that Antithrombin decreased more with pseudomonas & klebsiella while protein C decreased more with staph aureus& klebsiella. While **Barton et al. (2000)** found that their levels are decreased more with gram negative bacteria. Also **Abosalem, et al. (2009)** found that Antithrombin and protein C levels are decreased irrespective to the type of the microorganism that causes neonatal sepsis.

These findings prove that every neonatal unit has its own pattern of microorganisms which change from time to time and antimicrobial combinations should be altered according to culture results.

In the present study we found that Antithrombin and protein C levels are decreased in late onset sepsis, Anti-thrombin in Suspected Sepsis was (54.9 ± 10.7)% & in Confirmed Sepsis was (35.7 ± 9.05) % while Protein C in Suspected Sepsis was (41.2 ± 8.5) % & in Confirmed Sepsis was (15.3 ± 6.4) % with highly significant difference between studied groups.

El Beshlawy et al. (2010) showed marked decrease in the level of the physiologic inhibition system of coagulation including antithrombin, protein C, and protein S in 100% of cases, compared to the control group. **Mathieu et al. (2006)** found that

that a fall in the levels of protein C and antithrombin may identify patients at risk of developing sever sepsis and multisystem failure. The decrease in protein C and antithrombin also seems to occur early in the disease process. Protein C and Antithrombin could thus be useful in the evaluation of the septic patient.

This agree with **Lauterbach et al. (2006)** who have also highlighted the importance of plasma antithrombin and protein C levels in early recognition of late-onset sepsis in newborns and mentioned that protein C may also have a prognostic value, because of the high statistical significance (p .0016) between plasma protein C functional level and the risk of death . While other studies **Abosalem, et al. (2009)** found that Antithrombin and protein C levels are decreased irrespective to the onset of sepsis (early or late onset).and this agree with **Betul et al. (2006)** who found that initial Antithrombin level of patients confirmed to have sepsis by clinical and laboratory findings were determined to be significantly lower than that of patients who had negative laboratory findings irrespective to time of sample.

In our study we found that the prognosis of disease is bad in patient with lower levels of Antithrombin and protein C compared to the suspected & control group. This agree with **Choi Q et al. (2014)** who stated that protein C exhibit best discriminating power for overt-DIC among anticoagulant proteins. Antithrombin and protein C related with DIC score and showed significant prognostic power, especially in patients with sepsis/severe infection and agree with **Abosalem, et al. (2009)** and this agree with **Betul et al. (2006)** who studied the prognostic value of Antithrombin , fibrinogen and platelet count. It revealed that the only independent variable that had a significant impact was Antithrombin level and an increase of one unit in Antithrombin levels decreased the risk of mortality by a factor of 0.5.

In our study As regard to Antithrombin Using ROC curve, it was shown that Anti-thrombin can be used to discriminate between patients with confirmed sepsis and patients with suspected sepsis at a cutoff level of < 42.5, with 76.7% sensitivity, 90% specificity, 88.5% PPV and 79.4% NPV (AUC = 0.91, p-value < 0.001). **Betul et al. (2006)** found that sensitivity of Antithrombin was 92.3 % while specificity was 61.9%, positive predictive value (PPV) and negative predictive value (NPV)

were 60.0% and 92.8% respectively.

In our study As regard to Protein C Using ROC curve, it was shown that protein C can be used to discriminate between patients with confirmed sepsis and patients with suspected sepsis at a cutoff level of < 28, with 100% sensitivity, 96.7% specificity, 96.8% PPV and 100% NPV (AUC = 0.99, p-value < 0.001).Choi Q et al (2014) found that The AUCs (95%CI) were 0.676 (0.586-0.758), 0.744 (0.657-0.818), for antithrombin, protein C. Among them, the AUCs showed significant difference (P<0.05).

In our study we found mortality incidence was 13.3% in suspected sepsis & 36.7% in confirmed sepsis. **Abosalem, et al. (2009)** found that mortality incidence was 43% of the septic neonates were died, while 57% were alive. While **Lauterbach et al. (2006)** found that 43.3% live 33.3% died with DIC 23.3 % died with no DIC.

CONCLUSION

Anti-thrombin and Protein C have high predictive value in diagnosis of LOS as their level were significantly lower in neonates with sepsis, either confirmed or suspected. The lowest values of plasma AT and PC were observed in neonates who had died in the course of sepsis. Antithrombin and protein C are more reliable markers of neonatal sepsis versus other parameters of sepsis as TLC and I/T ratio. They are also a quick diagnostic parameters of sepsis neonatorum compared to blood culture for example. Measurement of plasma AT and PC levels, together with C-reactive protein and total leukocyte count with differential, may facilitate the recognition of sepsis.

Also high Anti-thrombin and Protein C levels have good prognostic value while marked decrease in Anti-thrombin and Protein C levels has bad prognosis.

Recommendations:

- Anti-thrombin and Protein C should be routinely measured in any case of neonatal sepsis.
- Wide scale study for use of protein c is needed in severe late onset sepsis as add on therapy.

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مستويات مضاد الثرومبين و بروتين سى في الدم فى الكشف المبكر عن الإنتان الوليدي المتأخر عند الأطفال الذين تم حجزهم بوحدة الرعاية المركزة لحديثى الولادة بمستشفى بنها التخصصى للأطفال

أ.د خالد محمود زايد*، د عمرو حميده مصطفى*، د أحمد عبد المعز علي سعد**

أ.د مصطفى عبد العظيم مصطفى*، أحمد أمين حامد حامد* (بكالوريوس الطب والجراحة)**

***قسم طب الاطفال، ****قسم الباثولوجيا الإكلينيكية، كليه الطب، جامعةالازهر**

*****قسم طب الاطفال، كليه الطب، جامعة بنها**

يعتبر الإنتان الوليدى البكتيرى من أهم أسباب المرض والوفاة فى الأطفال حديثى الولادة كما يعتبر الإنتان الوليدى البكتيرى من الأمراض الخطيرة والأطفال الذين يتعافون منه يعانون من مشاكل عصبية نتيجة تأثر الجهاز العصبى وكذلك يعانون من صدمة (هبوط فى الدورة الدموية) نتيجة تأثر أنسجة الرئة أو الإرتفاع المستمر فى ضغط الشريان الرئوى.

إن نقص خصوصية العلامات الحيوية و الفحوصات التى تحدد الإنتان الوليدى البكتيرى يمثل مشكله للأطباء وتعتبر الطريقة الأمثل للتشخيص هى أخذ مزرعة من سوائل الجسم وخاصة الدم.ولكن غالبا ما تحتاج المزرعة حوالى 48 إلى 72ساعة قبل أن تظهر النتائج وبالإضافة الى ذلك فإن المزارع تعانى من نقص فى الحساسية.

من الأشياء المعتبرة كمقياس مفيد فى التشخيص المبكر للإنتان الوليدى البكتيرى هو قياس العدد الكلى لكرات الدم البيضاء وقياس نسبة خلايا الدم البيضاء المتعادلة الغير ناضجة/ العدد الكلى لخلايا الدم البيضاء المتعادلة وكذلك قياس بروتين سى التفاعلى (سى آر بى).

يقل مستوى كلاً من مضاد الثرومبين وبروتين سى فى حالات الإنتان الوليدى البكتيرى وعندما يقل فإنه ينبئ بزيادة نسبة الوفاة.

إن قياس نسبة كلاً من مضاد الثرومبين وبروتين سى وخاصة بروتين سى يُسهل من التعرف على الإنتان الوليدى البكتيرى مع الأخذ فى الإعتبار أن بروتين سى له أهمية تنبؤية.

إن هذه الدراسة تهدف إلى معرفة الأهمية التشخيصية والتنبؤية لكل من مضاد الثرومبين وبروتين سى فى حالات الإنتان الوليدى البكتيرى.

طرق البحث: وقد اشتملت هذه الدراسة على 90 طفل حديثى الولادة بين 3-30 يوم و موزعين كالأتى:

- **المجموعة الأولى:** 30 طفل حديثى الولادة كفريق منظم لايعانون من الانتان الوليدى.
- **المجموعة الثانية:** 30 طفل حديثى الولادة و يعانون من اشتباه الإنتان الوليدى البكتيرى.

- المجموعة الثالثة: 30 طفل حديثى الولادة و يعانون من الإنتان الوليدى البكتيرى المؤكد بواسطة ايجابية المزرعة الدموية للبكتريا.

وقد خضعت المجموعات لدراسة التاريخ الطبى قبل واثناء وبعد الولادة والكشف الدقيق مثل قياس العلامات الحيوية ووجود صعوبة بالتنفس أو وجود أى علامة من علامات الإنتان الوليدى.

تم سحب المعامل الروتينية من صورة دم كاملة وسى آر بى و معادن الجسم كالصوديوم والكالسيوم والبوتاسيوم ووظائف الكبد والكلى وتم سحب مزارع الدم و تم سحب مزارع البول والسائل النخاعى فى حالة الاحتياج اليهم.

وقد أخذت عينة من كل طفل لقياس نسبة كلآ من مضاد الثرومبين وبروتين سى وتمت متابعة الأطفال من حيث تحسن الحالة الإكلينيكية أو عدم التحسن والوفاة ومقارنة ذلك بنسبة كلآ من مضاد الثرومبين وبروتين سى.

استنتاجات البحث:

- كانت نسبة الاطفال الذكور الى الاناث 1:2.
- كانت نسبة ال بروتين سى التفاعلى ذو دلالة إحصائية عالية بين المجموعات.

- كانت نسبة خلايا الدم البيضاء المتعادلة الغير ناضجة / العدد الكلى لخلايا الدم البيضاء المتعادلة اكثر من 0.2 مما يرجح او يدل على الإنتان الوليدى البكتيرى.

- كانت اكثر ميكروب موجود فى المصابين هو بكتيريا كليبسييلا (66.7%), ثم البكتريا المكورة العنقودية (23.3%) ثم البكتريا المكورة العنقودية المقاومة للميثيسيلين (6.7%) ثم الزائفة البكتيرية (3.3%).

- كانت نسبة مضاد الثرومبين اكثر انخفاضا مع بكتيريا الزائفة البكتيرية و كليبسييلا.

- كانت نسبة بروتين سى اكثر انخفاضا مع بكتيريا كليبسييلا و البكتريا المكورة العنقودية.

- أظهرت هذه الدراسة أن نسبة كلاً من مضاد الثرومبين وبروتين سى كانت أكثر انخفاضا فى الاطفال المصابين المؤكدين عن الاطفال المشتبه فى اصابتهم بالإنتان الوليدى البكتيرى.

- حيث كان المتوسط ل مضاد الثرمبين (54.9 فى مجموعة اشتباه الإنتان الوليدى البكتيرى و كان 35.7 فى مجموعة الإنتان الوليدى البكتيرى المؤكد).

- وكان متوسط بروتين سى (41.2 فى مجموعة اشتباه الإنتان الوليدى البكتيرى و كان 15.3 فى مجموعة الإنتان الوليدى البكتيرى المؤكد).

- أظهرت هذه الدراسة أن إنخفاض نسبة كلاً من مضاد الثرومبين وبروتين سى كانت أكثر فى الأطفال الذين توفوا عنهم فى الأطفال الذين على قيد الحياة حيث كانت نسبة الوفيات (13.3% فى مجموعة اشتباه الإنتان الوليدى البكتيرى و كان 36.7% فى مجموعة الإنتان الوليدى البكتيرى المؤكد).

توصيات البحث:

- علي ضوء هذه النتائج نوصي بأن مضاد الثرومبين وبروتين سى من الدلالات المهمة الموجودة في الدم ويمكن أن يستخدم في تشخيص الإنتان الوليدى البكتيرى.ويمكن إستخدامه في التنبؤ للحالة من حيث تحسن الحالة الإكلينيكية أو عدم التحسن والوفاة.

- لابد من عمل دراسات متعددة على مجموعة كبيرة من حالات الإنتان الوليدى البكتيرى لمساندة هذا البحث لإثبات إنخفاض نسبة كلاً من مضاد الثرومبين وبروتين سى في هذه الحالات ولإستخدامه من ضمن التحاليل والفحوصات التي يتم عملها كأبحاث روتينية في هذا المرض.