Procalcitonin As An Early Marker Of Neonatal Sepsis

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Abstract : Neonatal sepsis is one of the major health problems throughout the world, the incidence of neonatal sepsis is 10 in 1000 live births, early diagnosis is complicated as early signs is minimal and similar to those of various non-infectious disease. Availability of laboratory tests provides accurate and rapid diagnosis of the disease would be of paramount importance in improving the outcome of this challenge problem. Procalcitonin PCT is one of calcitonin precursors, microbial infection result in ubiquitous increase in CALCI gene expression and subsequent release of calcitonin precursors from all tissue and all cell type throughout the body. It can be used a s a tool for diagnosis of bacterial disease in neonates and children . It can be detected in plasma 2 hours after injection of endotoxinTo assess the role of Procalcitonin as a marker in the early diagnosis, treatment and follow up of neonatal sepsis. The study carried out in NICU in Ahmed Maher Teaching Hospital including 3 groups (10 neonates in each group) , group 1 (proven sepsis) group 2 (suspected sepsis), group 3 (clinical sepsis) with total study size 30 neonates. Complete blood count, ESR, CRP, blood culture, Procalcitonin level, and other laboratory test as indicated were done at day 1 before start of treatment and day 5 after treatment. Data was analyzed using appropriate method. 66.6% had early onset sepsis, 33.4% late onset sepsis, Group I (proven sepsis) 5 cases were positive for E. Coli. 2 cases positive for staphyllococusaureus and 3 cases positive for Klebsiella. Procalcitonin level in 1st sample in group 1 (proven sepsis) was positive in 1 case and strong positive in 9 cases. In group 2 (suspected sepsis) 3 cases were negative, 5 cases were positive, and 2 strong positive. In group 3 (clinical sepsis) 3 cases were negative, 1 case was weak positive, and 6 cases were negative. While in 2nd sample (5 days after treatment), Group 1 (proven sepsis) 2 patients became negative and 8 became lower concentration, Group 2 (suspected sepsis) 8 patients became negative, Group 3 (clinical sepsis) all patient became negative Procalcitonin level is a useful marker in the early diagnosis and treatment and follow up of neonatal sepsis.

Introduction:

Neonatal sepsis is one of the major health problems throughout the world, every year an estimated 30 million newborn acquire infection and 1-2 million of them die **(3)**.Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection accompanied by bacteremia in the first month of life **(13)**. The incidence of sepsis is estimated to be 10 in 1000 live births, and the risk increased by three to four times for newborns weighing less than 1500 gram. As early diagnosis of neonatal sepsis is complicated, early signs of neonatal sepsis is minimal and similar to those of various non infectious diseases, blood culture results are not available until at least 48 – 72 hours after specimen reach the laboratory and other tests such as leukocytic count, immature total neutrophils ratio, and C reactive protein are unable to provide a definitive early diagnosis **(4)**.

Therefore availability of a laboratory test provides accurate and rapid diagnosis of the disease would be of paramount importance in improving the outcome of this challenge problem.Procalcitonin is a 116 amino acid peptide and one of the precursors of the calcitonin, the physiological function of calcitonin remains unknown.

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No disorders attributable to either an excess or deficiency of calcitonin have been identified. Microbial infection induced a ubiquitous increase in CALCI gene expression and subsequent release of calcitonin precursors from all tissue and all cell types throughout the body **(16).**

Procalcitonin is a useful additional tool for the diagnosis of bacterial diseases in the neonates and children **(16).**

In bacterial infection, Procalcitonin increases from concentration in picgram (below the detection level of current Procalcitonin assay) to plasma level concentration ranging from 1–1000ng/ml. this increase often correlate with severity of the disease and with mortality. Procalcitonin can be detected in the plasma 2 hours after the injection of endotoxins, within 6-8 hours Procalcitonin concentration rise and a plateau is reached after approximately 12 hours and decrease to its normal values after 2-3 days **(16)**.

Procalcitonin and TNF-α are the best markers in the diagnosis of the neonatal sepsis and these markers are also valuable in following the effectiveness of treatment and determining the prognosis of the disease **(5) .**

Patients and Methods:

This prospective study was conducted on thirty neonates admitted for sepsis work up in NICU in Ahmed Maher

Teaching Hospital. Sepsis work up includes complete blood count (CBC), blood culture, erythrocyte sedimentation ratio (ESR), C- reactive protein (CRP). Other investigations such as urine analysis, CSF examination, and tracheal aspirate culture were done when needed.

Three distinct groups were defined, proven sepsis, suspected sepsis, and clinical sepsis.

- **Proven sepsis**: **(group1)** clinical signs and symptoms of sepsis plus a positive blood culture.
- **Suspected sepsis**: **(group 2)** clinical signs and symptoms of sepsis with negative blood culture and at least 2 positive screening test (CBC, CRP, ESR, or CXR).
- **Clinical sepsis: (group 3)** clinical signs and symptoms with negative bacterial culture and negative screening test.

Exclusion criteria:

1-Administration of antibiotic therapy before admission
2-Birth asphyxia
3-Aspiration syndrome
4-Laboratory finding suggestive of inborn error of metabolism
5-Congenital anomalies

Sample size 30 neonates (10 of each group), before starting antibiotic sample for CBC, CRP, ESR, Procalcitonin and cultures were collected (sample 1). This procedure repeated at day 5 after treatment with antibiotic (sample 2). Other additional tests were obtained when indicated.

Serum PCT was measured by using quantization Immune- Luminometry methods by Lumitest Kit (Brahms Diagnostic, Berlin, and Germany).

In this assay PCT $\geq$ 0.5ng/ml was accepted as pathogenic, PCT level 0.5 – 2 ng/ml, 2-10 ng/ml, $\geq$ 10 ng/ml (considered as weakly positive, positive, strong positive respectively) as recommended (16).

Statistical analysis:

We used SPSS version 16 for statistical analysis correlation between variables and statistical difference were analyzed using fisher exact , paired t test, ANOVA, chi – square test ,Monte Carlo and Wilcoxon test, , Correlation coefficient test . P-values of 0.05 were considered the cut -off value for significance , $\leq$ 0.001 will consider being highly significant.

Results:

Table (1) Descriptive data of studied neonates

	Groups	Mean	SD	Mini	Max	ANOVA	P value
Gestational age (weeks)	Group 1	32.5	2.89	30	38	0.758	0.47(NS)
	Group 2	33.2	2.79	31	38		
	Group 3	33.6	2.62	30	38		
Weight (grams)	Group 1	2800	434	2650	3050	0.556	0.58(NS)
	Group 2	2845	355	2700	3100		
	Group 3	2870	416	2725	3100		

There was no significant difference between study groups regarding to gestational age and weight ($p < 0.05$).

Table (2) show sex of patient of different study groups

Cases	Sex		Chi -Square	P value
	Male	Females		
Group 1	6	4	0.271	0.873 (NS)
Group 2	5	5		
Group 3	6	4		

No significant difference between study groups regarding to sex.

Table (3) show classification of cases according to onset of sepsis

	Early onset	Late onset
Number/ percent	20 (66.6%)	10 (33.4%)

Table (4): show result of sepsis screen test at time of admission in the three study group

Groups	ESR		CRP		WBCs		CXR	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Group I	4	6	4	6	4	6	8	2
Group2	2	8	0	10	3	7	3	7
Group3	6	4	8	2	6	4	10	0

Table (5) shows type of organism in blood culture in group 1 (proven sepsis)

Organism	Escherichia Coli	Staphylococcus aurous	klebsialla
Number of cases	5	2	3
Percentage	50%	20%	30%

Table (6): shows comparison between PCT level before and after 5 days of treatment in three different groups

	Group 1 (proven sepsis)		Group 2 (suspected sepsis)		Group 3 (clinical sepsis)	
	Before	After	Before	After	Before	After
Negative	0	2	3	8	3	10
Weak positive	0	5	0	0	1	0
Positive	1	3	5	2	6	0
Strong positive	9	0	2	0	0	0

In neonates with proven sepsis in spite of negative results of sepsis screening test, the results of PCT were positive in all patients.

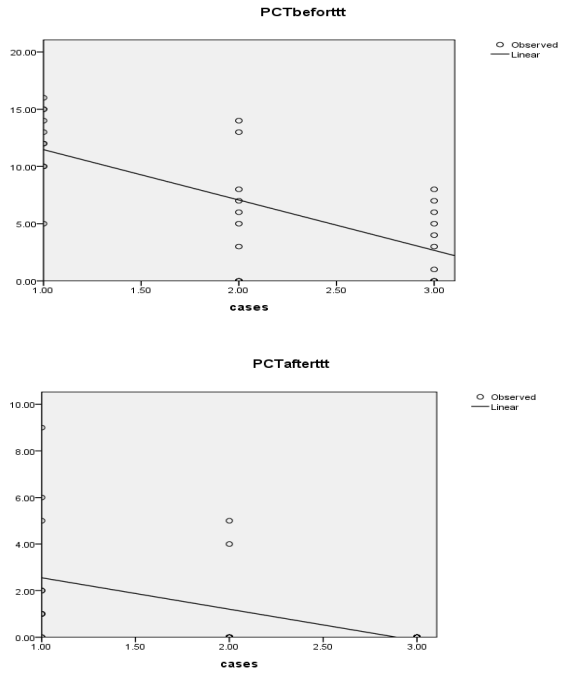
PCT after treatment (second sample taken after 5 days of treatment)

- Group I (proven sepsis) 2 patient become negative, 8 patient become lower concentration.
- Group 2 (suspected sepsis) 8 patient become negative
- Group 3 (clinical sepsis) all patient become negative.

Tab. (7) Correlation between PCT level and severity of sepsis before & after treatment

Cases group	r value	P value
PCT before ttt	0.68	0.000 (HS)
PCT after ttt	0.492	0.006 (S)

r = correlation HS= highly significant S= significant



Fig(1) showing significant increase of PCT with group 1 cases (proven sepsis) than group 2 (suspected sepsis) and group 3 (clinical sepsis)

Table (8) Comparison between PCT level before and after ttt in studied neonates

	Mean ng/ml	SD	Paired t test	P value
PCT before ttt	7.067	5.3623	6.964	0.000 (HS)
PCT after ttt	1.200	2.2804		

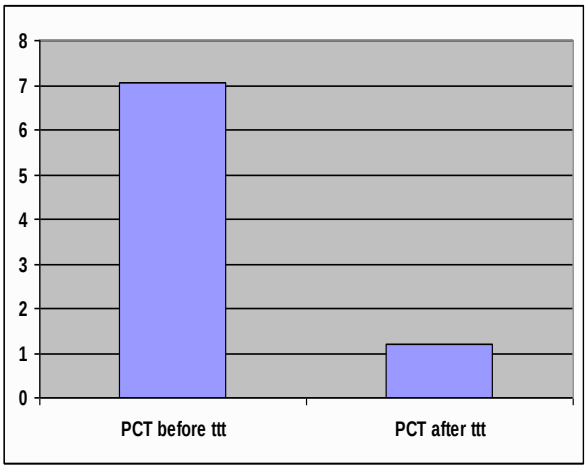


Fig. (2) Comparison between PCT level before and after ttt in studied neonates

Discussion:

In our study the Procalcitonin levels were remarkable high in neonates with proven sepsis;this is in agreement with result of several studies done before, such as **Monika (11)**.

In our study the serum PCT level was high in most of the patient before the initiation of the treatment but there was significant difference regarding the categories of the sepsis this is in agreement with **Naher (12), and Sakha (14) who** stated that values of PCT differed significantly in the different categories of sepsis indicating relation to the severity of sepsis.

In our study some cases of proven sepsis and suspected sepsis had a high level of PCT in spite of negative results of sepsis screening test this is in agreement with **Von Rossum (16)** who stated that increase in PCT occur more rapidly than the increase in CRP and PCT can be detected in plasma 2 hours after injection of endotoxins. Also **Mohammed (10)** suggested that PCT might be more reliable marker of infection than serum CRP or WBCs count in early diagnosis and response to antibiotic therapy of neonatal sepsis. Our result also was in agreement with **Koskal (8)** who stated that PCT was superior to the serum CRP level in term of early diagnosis of neonatal sepsis, in detecting the severity of the illness, and evaluation of the response to antibiotic treatment.

In our study serum PCT decreased significantly in all three sepsis groups which was dramatic decrease most evident in proven sepsis group this is in agreement with **Mohammed (10)** and **Koskal (8)**, who reported that after 7 days of treatment neonates who had achieved clinical recovery hand significantly lower serum PCT level than that of the same group at the beginning of the study. , and also in agreement with **Turner (15)** , who stated that serum level of PCT decreased significantly in all three groups which were most evident in proven sepsis group.

In our study there was 6 cases with positive blood culture with elevated PCT while CRP level was not elevated this is correlated with the studies done by **Mohammed (10) and Yadolla (2)** who concluded that serum level of PCT might be a more reliable marker of infection than serum level of CRP and WBCs count in the early diagnosis and response to antibiotic therapy.
Kawezynski (7) find that at onset of gram negative sepsis 14 out of 17 contaminated newborn had significantly increased PCT and CRP level but at the onset of gram positive sepsis only 18 out of 31 neonates with positive blood culture had increased CRP level and 28 of them had elevated concentration of PCT these difference was statistical significant. Also the usefulness of PCT as marker of 13 acute nosocomial infection in neonates is assessed by **Lopez (9)** in teaching hospital in Spain over one year and they concluded that serum PCT

concentration showed a moderate diagnostic reliability infection

Summary:
PCT concentration in our study was elevated in culture positive neonates and decrease with appropriate therapy, in some cases of culture positive babies other sepsis screening test were negative but the level of PCT was elevated.

Conclusion:
Procalcitonin level is a useful marker in early diagnosis of neonatal sepsis.

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