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Diagnostic Value of Procalcitonin in Well-appearing Febrile Children

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ABSTRACT

Background: Occult bacteremia (OB) means bacteremia without an obvious focus of infection. About 30 % of febrile children, three months to three years old have occult bacteremia, many children with occult bacteremia may appear relatively well. If occult bacteremia is neglected and not treated, it may be localized resulting in meningitis, pneumonia, cellulitis or septic arthritis. **Objective:** This study aimed to evaluate the estimation of serum procalcitonin (PCT) in determination of genuine bacterial contamination specifically intrusive bacterial disease in well-seeming febrile cases.

Subjects and methods: This cross-sectional study, which was conducted at Pediatrics Department of Zagazig University Hospitals from April 2016 to October 2016. This study was conducted on 37 cases with fever without source (FWS). All patients were subjected to detailed history taking, general examination and laboratory investigations included serum procalcitonin (PCT), complete blood picture (CBC), C-reactive protein (CRP) and blood culture.

Results: There was significant increase in WBCs among positive culture group than negative culture group. There was statistically significant increase in procalcitonin (PCT) among positive culture group than negative culture group. There were statistically significant positive correlation between PCT & CRP and PCT & TLC.

Conclusion: PCT shows the highest sensitivity and specificity for detection of cases compared to other parameters of infection.

Keywords: Occult bacteremia (OB), Procalcitonin (PCT), fever without source (FWS).

INTRODUCTION

Occult bacteremia (OB) means bacteremia without an obvious focus of infection. About 30 % of febrile children, three months to three years old have occult bacteremia, many children with occult bacteremia may appear relatively well. If occult bacteremia is neglected and not treated, it may be localized resulting in meningitis, pneumonia, cellulitis or septic arthritis **(1).**

Procalcitonin (PCT), which is the key precursor of calcitonin, has been reported to be a specific marker of bacterial infection, its cellular origin and its metabolic pathway is not known. PCT had been demonstrated to be released into the blood 3-6 hours after endotoxin injections into humans, thus the molecule seems to be closely dependent on the cytokine response against micro-organism **(2).** Procalcitonin, a propeptid of calcitonin devoid of hormonal activity, had been measured in various systemic inflammatory response syndromes including severe infections, burns and heat stroke. Plasma concentration of procalcitonin are very low in healthy individuals (< 0.1ug /L) and increase up to 1700 fold in respond to bacterial endotoxins. PCT had been described recently as a marker of infection that can help in the early diagnosis of bacterial neonatal infection and contributes to the differentiation of bacterial versus viral meningitis in children **(3)**.

It is found that the magnitude of the increase in procalcitonin concentration in systemic viral and localized bacterial infections is much smaller than that after systemic infections with bacteremia. Procalcitonin concentration decreases with antibiotic therapy **(4).** This study aimed to evaluate the estimation of serum procalcitonin (PCT) in determination of genuine bacterial contamination specifically intrusive bacterial disease in well-seeming febrile cases.

PATIENTS AND METHODS

This cross-sectional study carried out from April 2016 to October 2018 in Pediatrics Department, Zagazig University Hospitals. The study included 37 children with fever without source (FWS).

Ethical approval:

Written informed consent was obtained from every participant's parents and the study was approved by the Research Ethical Committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Sample Measure: Confidence Interval: 95%, Power: 80%. As the total number of well appearing febrile children attending to Pediatric Department, Zagazig University Hospitals is 360 cases per six months and predictive positive value of procalcitonin in prediction of serious bacterial infections is 70 %. So, sample size calculated to be 37 cases.

Inclusion criteria: Any youngster who had well-showing up with fever without core interest.

Exclusion criteria: Cases in which the physical examination performed on landing in the PED enabled the source of the fever to be recognized. Cases named not well showing up on entry to the PED; cases at first

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named well showing up however whose clinical circumstance in this manner compounded had incorporated. Cases who had a febrile in the PED, had judged to have fever at home without the utilization of a thermometer. Cases that had a febrile in the PED however in whom fever had affirmed by estimation of the baby's temperature at home had incorporated. Cases in whom PCT had not measured or its esteem had not recorded in the case's therapeutic record and those in whom a blood culture had not performed. All patients were subjected to detailed history taking, general examination and laboratory investigations including serum procalcitonin (PCT). The PCT levels in the peripheral blood of patients were analyzed. The PCT was tested using a chemiluminescent immunoassay with an automatic chemiluminescence apparatus (Snibe Diagnostic MAGLUMI 1000) and diagnostic kits (both provided by Shenzhen New Industries Biomedical Engineering Co., Ltd, China). Complete blood picture (CBC) were done on automated cell counter (coulter) with the differential count done on Leishmania-Giemsa-stained peripheral blood film. Serum C-responsive protein (CRP) level. Quantitative measurement of the level of C-reactive protein (CRP) using qualitative latex agglutination test. Blood culture by BaCT/ ALERT 3D 60.

Statistical Analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 24. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute frequencies and were compared using Chi square test and fisher exact test when appropriate. Kolmogorov-Smirnov (distribution-type) tests were used to verify assumptions for use in parametric tests. To compare continuous quantitative data of two groups, Mann Whitney test (for non-normally distributed data) and independent sample t test (for normally distributed data) were used. The level statistical significance was set at 5% ($P \leq 0.05$).

RESULTS

Table (1): demographic data of the studied cases

		Rang	Mean ± SD
Age (month)		3.0 - 36.0	16.54 ± 10.12
		No.	**%**
Sex	**Female**	18	48.6
	Male	19	51.4
		No.	**%**
Culture group	**Positive culture group**	26	70.3
	Negative culture group	11	29.7

Table (1) showed that the mean of age was 16.54 ± 10.12 months. Regarding sex, the percentage of females was 48.6 % and that of males was 51.4 %. The percentage of positive culture group was 70.3 % and that of negative culture group was 29.7 %.

Table (2): Comparison between positive culture group and negative culture group regarding clinical presentation

			Positive culture group	Negative culture group	Total	P. value
Fever	**Yes**	**No.**	26	11	37	1
		%	100.0 %	100.0%	100.0 %	
Cough	**No**	**No.**	23	10	33	.827
		%	88.5%	90.9%	89.2%	
	Yes	**No.**	3	1	4	
		%	11.5%	9.1%	10.8%	
Sore	**No**	**No.**	25	11	36	.510
		%	96.2%	100.0%	97.3%	
	Yes	**No.**	1	0	1	
		%	3.8%	.0%	2.7%	
Dysurea	**No**	**No.**	24	10	34	.887
		%	92.3%	90.9%	91.9%	
	Yes	**No.**	2	1	3	
		%	7.7%	9.1%	8.1%	
Convulsion	**No**	**No.**	24	11	35	.344
		%	92.3%	100.0%	94.6%	
	Yes	**No.**	2	0	2	
		%	7.7%	.0%	5.4%	
Creps	**No**	**No.**	26	11	37	1
		%	100.0 %	100.0%	100.0 %	
Abd pain	**No**	**No.**	23	11	34	.240
		%	88.5%	100.0%	91.9%	
	Yes	**No.**	3	0	3	
		%	11.5%	.0%	8.1%	

Table (2) showed that there was no statistically significant difference between positive culture group and negative culture group regarding fever, cough, sore, dysuria, convulsion, creps and abdominal pain.

Table (3): Comparison between positive culture group and negative culture group regarding laboratory investigation

		Positive culture group	Negative culture group	P. value
TLC (µl)	**Mean ± SD**	13.19 ± 2.73	11.273 ± 3.22	0.032
Neut (mcL)	**Mean ± SD**	51.15 ± 11.658	40.36 ± 9.88	0.043
Lymph%	**Mean ± SD**	42.69 ± 9.72	47.91 ± 10.42	0.435
PLT (mcL)	**Mean ± SD**	161.19 ± 37.012	256.00 ± 60.91	0.006
CRP (mg/L)	**Mean ± SD**	23.99 ± 4.67	16.60 ± 3.07	.048
PCT	**Mean ± SD**	9.04 ± 2.19	5.26 ± 1.06	0.018

Table (3) showed that there was statistically significant increase in TLC among positive culture

group than in negative culture group. There was statistically significant increase in neutrophils among positive culture group than in negative culture group. There was no statistically significant difference between positive culture group and negative culture group regarding lymphocytes. There was statistically significant decrease in PLT among positive culture group than in negative culture group. There was statistically significant increase in CRP among positive culture group than in negative culture group. There was statistically significant increase in PCT among positive culture group than in negative culture group.

Table (4): Regression analysis for prediction of cases

		Sig.	OR	95% C.I for EXP(B)	
				Lower	Upper
Step 1[a]	**TLC**	0.032	**1.001**	.781	2.216
	Neut	0.043	**.865**	.730	1.024
	Lymph	0.435	**.922**	.781	1.088
	PLT	0.006	**1.018**	.987	1.049
	CRP	0.048	**.922**	.811	1.048
	PCT	0.018	**1.122**	.894	1.407

OR, odds ratio; CI, confidence interval.
Logistic regression test was used

Logistic regression analysis was conducted for prediction of cases using TLC, neutrophils, lymphocytes, PLT, CRP and PCT. PCT was more accurate for diagnosis of cases than other variables because the odds ratio for PCT was higher than odds ratio for other variables (Table 4).

Table (5): Accuracy of PCT in diagnosis cases

			Positive culture group	Negative culture group
PCT	**Positive >6**	**No.**	16	3
		%	84.2%	15.8%
		%	61.5%	27.3%
	Negative <6	**No.**	10	8
		%	55.6%	44.4%
		%	38.5%	72.7%

Table (5) showed that the procalcitonin as a test for diagnosing of cases, it revealed that sensitivity = 61.5%, specificity = 72.7%, predictive value for +ve = 84.2%, predictive value for –ve = 44.4% and Accuracy = 64.8%.

DISCUSSION

This study showed that, the percentage of positive culture group was 70.3 % and negative culture group was 29.7 %. In the current study, there was no significant difference between both groups concerning age ($p > 0.05$). These findings are comparable with the result of study made by **El-Gendy *et al.*** [5] who reported that the value of apolipoprotein A1 (Apo A1) in the diagnosis and prognosis of pediatric sepsis showed no significant difference in patients and controls in terms of age.

This study showed that fever and signs of respiratory distress were the most common. This is in partial agreement with **El-Gendy *et al.*** [5] who found that clinical manifestations in the patient group were tachypnea (80%), distention (70%), intercostal retraction (65%), lethargy (52.5%), temp instability (45%), hepatomegaly (45%), hypoglycemia (37.5%), weak pulse (20%), irritability (15%), seizure (10%), grunting (10%), cyanosis (7.5%), bloody stool (5%), and diarrhea (5%). Also, this comes in agreement with **Payaslı *et al.*** [6] who found that respiratory distress (R.D) was the most common clinical presentation (80%) followed by lethargy and hypotonia.

Regarding CBC, our results revealed that, there was significant increase in WBCs among positive culture group than in negative culture group. Our result agrees with **El-Mazary *et al.*** [7] who found that WBCs was significantly higher between cases with pediatric sepsis than in control. **Mehta *et al.*** [8] reported that increase TLC could be possibly due to release of various growth factors and cytokines as G-CSF, GM-CSF, IL-3, IL-6, which stimulate bone marrow. Band cells may increase due to rapid production.

In the present work, the mean count of platelets was significantly lowered among positive culture group than in negative culture group. This agrees with **Rass *et al.*** [9] who studied platelets in neonatal sepsis. They found statistically significant decrease in sepsis group than in the control group.

Thrombocytopenia is one of the most common complications of neonatal sepsis; this may be attributed to bone marrow depression, consumption coagulopathy, platelet sequestration, or a combination of these processes. Thrombocytopenia is considered one of the hematological parameters of severity of neonatal sepsis, but a normal platelet count does not exclude sepsis [10].

Regarding CRP, there was significant increase in positive culture group than in negative culture group. This agrees also with **Higazi *et al.*** [11] who aimed to evaluate the diagnostic and prognostic performances of urinary interleukin-18 (uIL-18) and serum amyloid A (SAA) in pediatric sepsis parallel to C- reactive protein (CRP). Their study was conducted in Minia University Hospital as well as Qena University hospital (Egypt). They demonstrated that CRP was statistically significantly higher in septic group than in non-septic ($p < 0.001$). This also is in agreement with **Krishnaveni *et al.*** [12] who found that CRP was higher among neonatal sepsis than in control group. These results are in agreement with **Boraey *et al.*** [13], and **Nora *et al.*** [14]. They found that CRP was the most common laboratory test that can be accurate for the diagnosis of sepsis. It is easily measurable and more affordable. CRP can be conveniently used as a marker for the diagnosis of neonatal sepsis, especially with poor resources.

This study showed that, there was statistically significant increase in procalcitonin (PCT) among

positive culture group than among negative culture group. These results are in agreement with **Mohsen and Kamel [15],** who aimed to assess the role of procalcitonin (PCT) as a marker in the early diagnosis of pediatric sepsis. They found that mean levels of PCT in neonates with sepsis were significantly higher than in the control group (p=0.0001). This is in agreement with **El Wakeel *et al.* [16]** who found that there was a highly statistically significant difference between cases and control regarding PCT level, which was higher in cases, with P less than 0.001. These results could be explained by the fact that inflammation stimulates the increase in the secretion of PCT in serum. Furthermore, **Gomez *et al.* [17]** who found high PCT in infants < 3 months with fever without source.

This study demonstrated that there were statistically significant positive correlation between PCT and CRP. This agrees with **Mohsen and Kamel [15]** who found that, there was a significant positive correlation between PCT and CRP, (r=−0.55, p=0.001). In contrast, a study by **Wang *et al.* [18]** showed insignificant correlation between PCT and CRP.

This study showed that there were statistically significant positive correlation between PCT and TLC. This agrees with **Mohsen and Kamel [15]** who found insignificant correlation between PCT and TLC among the children with sepsis (r=−0.20, p > 0.05).

In our study regarding the procalcitonin as a test for diagnosing of cases it revealed that sensitivity was 61.5%, specificity was 72.7%, predictive value for +ve was 84.2%, predictive value for –ve was 44.4% and accuracy was 64.8%. CRP as a test for diagnosing of cases, revealed that sensitivity was 53.8%, specificity was 54.5%, predictive value for +ve was 73.7%, predictive value for –ve was 33.3% and accuracy was 59.4%. This agrees with **Mohsen and Kamel [15]** who found that the sensitivity of PCT for the diagnosis of neonatal sepsis was 80%, the specificity was 85.7%, its PPV was 84.8%, and NPV was 81.1%. The sensitivity of CRP was 72.9%, the specificity was 100%, its PPV was 93.2%, and its NPV was 69.7%. These results found that PCT was more sensitive than CRP. **Hasan *et al.* [19]** added that the advantages of PCT over CRP are that its level increases mainly in bacterial infection, and its normal level is rapidly restored after antibiotic therapy. So, PCT is superior to CRP in the early diagnosis of pediatric sepsis, detecting sepsis severity and evaluating the antibiotic treatment response. Inconsistent with our results, **Janota *et al.* [20]** and **Mamdouh *et al.* [21]** concluded that the lower specificity of PCT could be related to the multi-organ dysfunction of the neonates who did not have sepsis.

CONCLUSION

PCT showed the highest sensitivity and specificity for detection of cases compared to other parameters of infection. It is recommended to do PCT in sepsis screen for fever in well appearing children.

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