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Original Article

Role of Procalcitonin in Evaluation of Urinary Tract Infection in Children

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ABSTRACT

Background: Febrile UTI is a common problem among children. The distinction between acute pyelonephritis and lower UTI is very important, because renal infection may cause parenchymal scarring and thus requires more aggressive investigations and follow-up monitoring. The clinical findings and laboratory markers such as leukocyte count and CRP do not reliably distinguish acute pyelonephritis from lower UTI especially in infants and young children. The gold standard for distinguishing acute pyelonephritis from lower UTI and to asses renal scaring is by using dimercaptosuccinic acid (DMSA) scan, which is very expensive, not available in all centers and exposes the patients to radiation.

Objectives: To determine procalcitonin (PCT) level in children with UTI to evaluate it as a marker for early diagnosis and differentiation between upper and lower UTI.

Methods: This study was carried on 30 patients with UTI, 8 males and 22 females with mean age 7.7 ± 2.5 years. They were divided into 2 groups: 12 patients with upper UTI and 18 patients with lower UTI. Complete urine analysis, urine culture and sensitivity, CBC, CRP, renal function tests and PCT level were done for all patients. CRP, PCT and urine culture and sensitivity were repeated again after treatment. Ten healthy children matched for age and sex served as controls.

Results: The mean PCT level was significantly higher in patients with UTI than controls (1.67 ± 0.9 ng/ml vs 0.37 ± 0.2 ng/ml, $p < 0.001$). Also PCT level was significantly higher in cases of acute pyelonephritis than lower UTI (2.38 ± 1.02 ng/ml vs 1.19 ± 0.2 ng/ml, $p < 0.01$). After treatment PCT decreased significantly, but was still significantly higher in acute pyelonephritis than lower UTI (1.02 ± 0.38 ng/ml vs 0.59 ± 0.23 ng/ml, $p < 0.01$). The sensitivity and specificity for PCT were 86.67% & 90% respectively with positive and negative predictive values of 96.29% & 69.92% respectively. For CRP, the sensitivity and specificity were 66.67% & 70% respectively, with positive and negative predictive values of 86.96% & 41.18% respectively. After treatment still 6 patients with acute pyelonephritis had significantly higher levels of PCT (1.2 ± 0.67 ng/ml vs 0.37 ± 0.2 ng/ml, $p < 0.01$) than the control which means renal parenchymal affection.

Conclusions: Serum PCT levels may be a sensitive and specific measure for early diagnosis of acute UTI and differentiation between upper and lower UTI. Also PCT can help in determination of the severity of renal parenchymal involvement and scarring. So we recommend imaging studies as DMSA if serum PCT level is still high after 2 weeks of proper treatment.

INTRODUCTION

Febrile urinary tract infection is a common problem in children[1]. By the age of 7 years approximately 8% of girls and 2% of boys will have had at least one attack of urinary tract infection. Transient damage to the kidney occurs in approximately 40% of children affected and permanent renal damage occurs approximately in 5% of cases[2], which requires more aggressive investigations and follow-up monitoring[3].

Renal scaring is worse in children who

developed their first attack of infection at a young age, had recurrent urinary tract infection and where there is a delay in diagnosis and treatment or where there is vesicoureteric reflux[4].

The clinical findings and laboratory markers such as serum leukocyte counts and CRP do not reliably distinguish acute pyelonephritis from lower urinary tract infection especially in infants and young children[1]. Also in most cases of acute pyelonephritis, ultrasonic images of the kidneys appear normal[5].

The gold standard for distinguishing pyelonephritis from lower urinary tract infection is an abnormal dimercaptosuccinic acid (DMSA) scan which is very expensive, not available in every institution and exposes the patient to radiation[3]. Moorthy et al.[6] stated that DMSA renal scan is the technique of choice to assess renal scaring.

Acute pyelonephritis requires aggressive treatment[1], since failure of diagnosis and treatment of acute pyelonephritis properly can lead to chronic morbidity[7]. In absence of specific symptomology in children the diagnosis of acute pyelonephritis is a challenge particularly during infancy[8]. Procalcitonin is a new marker of bacterial infection[9]. Benador et al.[1], concluded from their study that procalcitonin is markedly increased in urinary tract infection with renal parenchymal involvement.

AIM OF THE WORK

The aim of our study was to measure procalcitonin level in children with urinary tract infection to evaluate its value as a marker for rapid early diagnosis, differentiation between lower urinary tract infection and acute pyelonephritis and identifying patients at risk of renal scaring who are in need of further imaging studies as DMSA.

SUBJECTS AND METHODS

This is a cross sectional study, carried out in the Pediatrics and Clinical Pathology Departments in Benha University Hospital. Thirty cases of urinary tract infection were enrolled in this study over the period from December 2003 to November 2004. Ten healthy children matched for age and sex served as controls.

Enrollment Criteria:

- Older children who could express their illness and who had their 1st attack of UTI were enrolled in this study. Criteria used for diagnosis of acute pyelonephritis included fever, malaise, nausea, vomiting, flank pain or tender renal angle, supported by ultrasonic findings (focal area of hypo or hyper-echogenicity). Patients with dysuria, suprapubic pain and frequency were diagnosed as lower UTI. The diagnosis was confirmed on the basis of positive urine culture, with a single microorganism at $\geq 10^5$ colony forming units/ml. Patients with known abnormalities or malformation of the urinary tract or with documented or suspected previous UTI were excluded from the study. Infants and young children who can not express their illness were excluded from the study.

All cases were subjected to:

1- Full history taking and thorough clinical examination. A midstream urine sample was collected for complete urine analysis and culture and sensitivity. Abdominal ultrasonography was done for all

patients. Blood samples were collected for renal function tests, CRP and CBC. Procalcitonin level was measured by immunoluminometric assay with 2 monoclonal antibodies (LUMI test, PCT; Brohms diagnostic, Hennigdrof BEI, Berlin)[8].

2- All cases of urinary tract infection were given the proper antibiotics according to culture and sensitivity results for 5 days in lower urinary tact infection and 2 weeks in acute pyelonephritis.
3- After completing the course of treatment, urine culture, CRP, procalcitonin level were done again.

Statistical analysis: results were expressed as means ± standard deviation of the mean. Differences between the two groups were analyzed by using "t" test.

RESULTS

Thirty cases suffering from urinary tract infection were enrolled in this study from January 2003 to December 2003 in Benha University Hospital. They were 8 males and 22 females with a mean age of 7.7 ± 2.5 years, together with 10 healthy children matched for age and sex serving as control.

According to clinical findings supported by ultrasonic changes (hypo or hyper-echogenicity) we divided the patients into 2 groups. The first one was the group of acute pyelonephritis (upper UTI), which included 12 patients. The second one was the group of lower UTI, which included 18 patients.

It is shown in Table (1) that UTI cases included 8 males representing 26.7% and 22 females representing 73.3% and this difference is significant statistically. Their mean age was 8.6 ± 2.52 year.

Table (2) shows the clinical and laboratory data for cases and their controls. The mean value for pus cells in the studied cases was 102 ± 23.9/mm^3 and 2.2 ± 0.6/mm^3 in the control and this difference is very highly significant statistically. Mean value for CRP was 37.3 ± 19.5 mg/L for the studied cases and 6 ± 3.2 mg/L in the controls with a very highly significant difference statistically. The mean level for procalcitonin was 1.67 ± 0.9 ng/ml and 0.37 ± 0.2 ng/ml for the studied cases and controls respectively. There is a very highly significant difference between cases and controls.

Table (3) shows that in the 30 patients where urine cultures were positive, 16 cases representing 53.33% were Escherichia–coli, 5 cases representing 16.67% were Staphylococcus aureus coagulase positive, Klebsiella in 4 cases representing 13.33% and Pseudomonas in 3 cases representing 10% and 2 cases were Proteus representing 6.67%.

Table (4) shows that the mean level of procalcitonin was significantly reduced after treatment. This level was 1.67 ± 0.9 ng/ml and 0.67 ± 0.36 ng/ml in all cases of UTI before and after treatment respectively. For upper UTI cases it was 2.38 ± 1.02 ng/ml and 1.02 ± 0.38 ng/ml before and after treatment respectively. For lower UTI cases it was 1.19 ± 0.2 ng/ml and 0.59 ± 0.23 ng/ml respectively. There is a highly statistically significant difference between pre- and post-treatment procalcitonin value for all the studied groups, ($p < 0.001$).

It is shown in Table (5) that the level of procalcitonin is higher in upper UTI cases

than in lower one pre- and post-treatment. It was 2.38 ± 1.02 ng/ml and 1.02 ± 0.38 ng/ml pre- and post-treatment for pyelonephritis, while it was 1.19 ± 0.2 ng/ml and 0.59 ± 0.23 ng/ml in lower UTI cases. So procalcitonin is significantly higher in the cases of pyelonephritis than in lower UTI though the level is significantly reduced after treatment but it is still significantly higher in upper UTI than in lower UTI ($p < 0.01$).

Table (6) shows that the specificity of procalcitonin was 90% while it was 70% for CRP. For sensitivity it was 86.67% for procalcitonin and was 66.76% for CRP. For positive predictive value and negative predictive value, it was 96.29% and 69.92% for procalcitonin, and was 86.96% and 41.18% for CRP respectively.

Table (7) shows that all cases become negative after completing the treatment for CRP value and culture results. However, 20% of cases still had a high level of procalcitonin after completing the treatment.

Table (8) shows that there is a significant difference in PCT level at the start of the study for cases of acute pyelonephritis, in which PCT level was still high after treatment, and the cases of acute pyelonephritis, in which their PCT level decreased significantly after treatment, 2.98 ± 0.33 ng/ml and 1.63 ± 0.83 ng/ml respectively, ($p < 0.01$).

Table (9) shows that there is a statistically significant difference for PCT level after treatment in cases of acute pyelonephritis, in which PCT was still high in 6 cases after treatment, when compared to controls, ($p < 0.01$).

Table 1: Sex differences of the studied groups and their controls.

Studies groups / Sex	Cases		Control		Z	P
	No.	%	No.	%		
Male	**8**	**26.7**	**5**	**50%**	**0.59**	**> 0.05**
Female	**22**	**73.3**	**5**	**50%**		
Z	**2.04**					
P	**< 0.05**					

Table 2: Clinical and laboratory findings in cases and their controls.

Studied group variables	Cases No. = 30 $\times \pm$ SD	Control No. = 10 $\times \pm$ SD	t	p
Age (years)	7.7 ± 2.5	8.6 ± 2.52	-0.87	> 0.05
Weight (kg)	35.1 ± 16.9	37.8 ± 14.1	-0.44	> 0.05
Height (cm)	134.9 ± 17.8	134.7 ± 20.2	0.03	> 0.05
Systolic BP (mm Hg)	95.3 ± 13.7	89.0 ± 7.4	1.5	> 0.05
Diastolic BP (mm Hg)	60.3 ± 9.3	60.0 ± 6.7	0.1	> 0.05
Temp °C	38.3 ± 0.7	37.0 ± 0	6.6	< 0.001
Creatinine (mg/dl)	1.27 ± 0.6	0.8 ± 1	3.68	< 0.01
Urea (mg/dl)	35.3 ± 12.3	29.0 ± 7.7	1.58	> 0.05
Pus cells/mm^3	102 ± 23.9	2.2 ± 0.6	16.55	< 0.001
CRP (mg/L)	37.3 ± 19.5	6.0 ± 3.2	-3.35	< 0.001
Procalcitonin (ng/ml)	1.67 ± 0.9	0.37 ± 0.2	5.51	< 0.001

Table 3: Results of urine culture in the studied cases.

Types of organism	No.	%
• Escherichia coli	16	53.33%
• Staph. aureus coagulase positive	5	16.67%
• Klebsiella	4	13.33%
• Pseudomonas	3	10%
• Proteus	2	6.67%

Table 4: Serum procalcitonin levels (ng/ml) in UTI cases before and after treatment.

Group	Pre treatment	After treatment	t	p
All cases (30)	1.67 ± 0.9	0.67 ± 0.36	5.09	< 0.001
Upper UTI cases (12)	2.38 ± 1.02	1.02 ± 0.38	9.71	< 0.001
Lower UTI cases (18)	1.19 ± 0.2	0.59 ± 0.23	5.45	< 0.001

Table 5: Serum procalcitonin level (ng/ml) in both upper and lower UTI cases before and after treatment.

Group / Procalcitonin	Upper UTI cases No. = 12	Lower UTI cases No. = 18	t	p
Before treatment	2.38 ± 1.02	1.19 ± 0.2	2.83	< 0.01
After treatment	1.02 ± 0.38	0.59 ± 0.23	2.53	< 0.01

Table 6: Sensitivity, specificity, positive and negative predictive values of procalcitonin and CRP.

Test	Sensitivity	Specificity	+ve Predictive value	-ve Predictive value
Procalcitonin	86.67%	90%	96.29%	69.92%
CRP	66.67%	70%	86.96%	41.18%

Table 7: Results of urine culture and sensitivity, CRP and procalcitonin levels after treatment.

	Procalcitonin level		CRP level		Culture	
	No.	%	No.	%	No.	%
Number of cases return to normal after treatment	24	80	30	100	30	100
Number of cases still higher than normal after treatment	6	20	0	0	0	0
Total	30		30		30	

Table 8: Serum procalcitonin level (ng/ml) in acute pyelonephritis cases before and after treatment.

Group / Procalcitonin	PCT still high after treatment No. = 6	PCT significantly decreased after treatment No. = 6	t	p
Before treatment	2.98 ± 0.33	1.63 ± 0.83	3.698	< 0.01
After treatment	1.2 ± 0.67	0.65 ± 0.58	1.694	> 0.05

Table 9: Serum procalcitonin level (ng/ml) after treatment in acute pyelonephritis cases versus control.

Group / Procalcitonin	PCT still high after treatment* (No. = 6)	PCT significantly decreased after treatment** (No. = 6)	Controls*** (No. = 10)
PCT X ± SD	1.2 ± 0.67	0.65 ± 0.58	0.37 ± 0.2
t	2.96	1.694	1.077
p	< 0.01	> 0.05	> 0.05
	* vs ***	* vs **	** vs ***

DISCUSSION

Febrile urinary tract infection is a common problem in children[1]. Bacterial infections of the urinary tract is a significant cause of illness in infants and children being the second in frequency to bacterial infection of the respiratory tract[10].

By the age of 7 years approximately 8% of girls and 2% of boys will have had at least one attack of urinary tract infection. Transient renal damage (scars) occur approximately in 40% of affected children and permanent renal damage occurs in 5% of cases which may lead to renal arterial hypertension and chronic renal failure[2].

Renal scaring is worse in children who developed their infection at a young age, had recurrent urinary tract infection, had vesicoureteric reflux and if there is a delay in diagnosis and treatment[4].

Many children under 7 years in the United Kingdom receive long term low dose of antibiotic prophylaxis while awaiting imaging investigations without clear evidence that this is effective in preventing renal scaring[11].

Rapid accurate diagnosis, early initiation of proper effective treatment and early detection of cases who are in need of further evaluation to detect renal scaring is a great challenge to pediatricians who are dealing with children suffering from urinary tract infection. The problem is more complicated by the absence of specific symptomatology to early diagnose pyelonephritis in infancy and young children[8].

Procalcitonin is a recent inflammatory marker which is markedly increased few hours after administration of endotoxins to human volunteers and in invasive bacterial infection[12].

Procalcitonin is a polypeptide present in the plasma of healthy subjects in minimal levels (< 0.5 ng/ml). Its half-life time in vivo is about 20-30 hours. Procalcitonin levels are rapidly increased in cases of severe bacterial infection and sepsis and reach a plateau after approximately 12 hours[13]. Procalcitonin stimulated by bacterial inflammation, is most likely not produced by C-cells of thyroid, but its possible origin may be the neuro-endocrine cells of the intestine[14]. Also serum procalcitonin levels showed rapid increase in children with sepsis, even in infants less than one year old, and they have a better prognostic value than CRP and neutrophil count[15].

- **Procalcitonin and diagnosis of urinary tract infection:**

Diagnosis of UTI was based on a positive urine culture with a single microorganism at $\geq 10^5$ colony-forming units/ml form a midstream urine sample.

The mean value for pus cells in the infected cases was $102 \pm 23.9/mm^3$ and $6 \pm 3.2/mm^3$ in the control group with a highly significant statistical difference ($p < 0.001$). Detection of pus cells only in urine is not a reliable method for diagnosis of UTI[7].

Our results showed that the mean level of procalcitonin in our cases of UTI was 1.67 ± 0.9 ng/ml and 0.37 ± 0.2 ng/ml for the controls, with highly significant difference ($p < 0.001$). Mean value for CRP was 37.3 ± 19.5 mg/L and 6 ± 3.2 mg/L in the infected cases and control group respectively and this difference is highly significant statistically ($p < 0.001$).

Our study showed that the sensitivity and specificity of procalcitonin (at a cut-off value of 0.7 ng/ml) were 86.67% and 90% respectively, and for CRP they were 66.67% and 70% respectively.

From our study it is clear that procalcitonin has the best sensitivity and specificity when compared to CRP. As stated form other studies it also has the advantage of being a rapid test and appears very early in the serum of infected persons, when compared to CRP which appears later on[13].

Quantitative urine culture and identification of the organism is still the standard laboratory procedure for definitive diagnosis of urinary tract infection[16]. Unfortunately culture may be negative in up to 70% in UTI cases. Also the low specificity can be explained by the fact that cultures may be positive in normal subjects without UTI because of contamination with mixed pre-urethral flora. This is in agreement with (Rushton[16] and Zaman et al.[7]).

Benador et al.[1], stated that CRP as an established marker for diagnosis of infection has a very low specificity and sensitivity in early diagnosis of urinary tract infection. They also stated that procalcitonin appears very early in the serum of infected persons compared to CRP which appears later on and also procalcitonin declined soon after elimination of the focus of infection.

Oberthaffer et al.[17] and Hatheril et al.[13], explained the low specificity of CRP by the fact that it can be induced by non-infective causes as repeated trauma or surgery.

- **Role of procalcitonin in differentiation between pyelonephritis and lower urinary tract infection:**

All cases of urinary tract infection at the time of diagnosis had a mean level of (1.67 ± 0.9 ng/ml) which was highly significantly elevated when compared to the healthy controls whose mean level was (0.37 ± 0.2 ng/ml). Procalcitonin was also significantly higher at the time of diagnosis in cases of pyelonephritis than cases of lower urinary tract infection with mean level (2.38 ± 1.02 ng/ml) & (1.19 ± 0.2 ng/ml) respectively and p value was < 0.01.

The significant elevation of procalcitonin in pyelonephritis is explained by renal parenchymal invasion[18].

Cases of lower urinary tract infection at the time of diagnosis showed that procalcitonin was about 3 folds more than that of healthy controls. Meanwhile pyelonephritis cases showed about 6 folds more for procalcitonin level than normal healthy controls. In agreement with our results are the studies done by Prat et al.[19] and Pecile et al.[3], who stated that procalcitonin level was higher in cases of pyelonephritis than lower UTI and it was higher in cases of pyelonephritis with renal parenchymal affection.

Follow-up parameters:

According to Elder[20], cases of lower urinary tract infection and pyelonephritis were given antibiotics according to results of culture and sensitivity for 5 days in lower UTI and 15 days in pyelonephritis.

CRP, urine culture and procalcitonin were repeated after the treatment course was completed. Results showed that culture and CRP became negative in all cases mean while procalcitonin remained significantly higher than normal healthy control level in 6 of 30 of cases representing, 20% of cases.

All the 6 cases were pyelonephritis cases. Also from the start these 6 patients had a significantly higher level for procalcitonin when compared to the other cases of upper UTI in which their procalcitonin level decreased significantly after treatment, ($p < 0.01$). Flores et al.[15] explained persistent elevation of procalcitonin in children with severe bacterial infection due to either persistence of infection (no response) or renal parenchymal invasion.

Pecile et al.[3] stated that there was no significant difference between CRP levels at admission for children with or without renal scars.

Ultrasound images of the kidneys appear normal in most cases of acute pyelonephritis[5].

After the other parameters of infection (culture & CRP) become negative, the infection has been controlled and the persistent elevation of procalcitonin after treatment is most probably due to renal parenchymal invasion. Also this is in agreement with the studies done by Han et al.[18] and Pecile et al.[3], who stated that significant elevation of procalcitonin in pyelonephritis is due to renal parenchymal invasion.

Conclusions and Recommendation:

- Procalcitonin may play a good role in early accurate diagnosis of urinary tract infection in infants and young children.
- Procalcitonin can be used to differentiate pyelonephritis cases from lower urinary tract infection. Elevated levels up to 3 folds more than the control goes with

lower urinary tract infection. Levels 6 folds or more than the control goes with pyelonephritis. To confirm its role in differentiation we recommend estimating the level of procalcitonin, 5 days and 2 weeks after treatment.

- If the level returns to normal after 5 days this means lower urinary tract infection and we have to stop treatment.
- If the level is still high after 5 days, this case could be pyelonephritis and it is recommended to complete the course of antibiotic treatment for 2 weeks.
- If the level is still high after 2 weeks, this means renal parenchymal affection and the patient needs to be refereed for further imaging studies as DMSA.

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