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Are Serum Procalcitonin and Interleukin-1 Beta Suitable Markers for Diagnosis of Acute Pyelonephritis in Children?

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Abstract: Rapid diagnosis of acute pyelonephritis is important because of its association with long-standing complications. This study was conducted to compare the reliability of serum procalcitonin (PCT) and interleukin-1 beta (IL-1β) with conventional laboratory parameters for diagnosis of acute pyelonephritis in children. Seventy nine children with urinary tract infection were divided into two groups based on the result of Tc-99m dimercaptosuccinic acid renal scan: acute pyelonephritis (n=33) and lower UTI (urinary tract infection) (n=46) groups. White blood cell (WBC) count, neutrophil count, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP), PCT and IL-1β concentrations of both groups were measured and compared. WBC count, neutrophil count, ESR, serum CRP, PCT and IL-1β concentrations were higher in acute pyelonephritis patients than in the lower UTI group ($P<0.05$). The sensitivity and specificity of serum PCT and IL-1β for diagnosis of acute pyelonephritis were 31, 84.7% and 27.2, 90% respectively (using a cut-point value of 0.5 ng/ml for PCT and 6.9 pg/ml for IL-1β). The sensitivity of PCT and IL-1β for diagnosis of acute pyelonephritis was less than that of conventional markers such as ESR and CRP. This study revealed that serum PCT and IL-1β are not good biologic markers for differentiating acute pyelonephritis from lower UTI. It seems that conventional inflammatory markers such as ESR and CRP besides the clinical findings are more reliable for the diagnosis of acute pyelonephritis in children.

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Introduction

Urinary tract infection (UTI) is common in children. By seven years of age, 8% of girls and 2% of boys will have at least one episode. The most common pathogen is *Escherichia coli*, accounting for about 85 percent of UTI in children (Williams et al., 2006). Acute pyelonephritis and lower UTI are two common forms of urinary tract infection in children. Lower UTI is usually without complications while acute pyelonephritis is severe form of disease and may result in renal scarring, hypertension and chronic renal failure (Hari et al., 2003; Hansson and Jodal, 2004). Previous studies have revealed that the rate of renal scarring due to acute pyelonephritis is 15–49% (Faust et al., 2009; Shaikh et al., 2010; Ayazi et al., 2011). Rapid diagnosis and promptly treatment of acute pyelonephritis can prevent renal scarring and subsequent complications. Although, clinical signs and symptoms such as fever, flank pain, dysuria and common inflammatory markers such as ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) can localize the site of UTI to some extent, but proper localization of UTI depend on the DMSA renal scanning which has been accepted as gold standard imaging method for diagnosis of acute pyelonephritis (Williams et al., 2006; Printza et al., 2012). However, this imaging device is not readily accessible in all health providing centers, and also exposes the patients to radiation. Also it may not distinguish between old scarring and acute parenchymal involvement (Gürgöze et al., 2005; Williams et al., 2006; Ifergan et al., 2012). As far as our knowledge and literature review is concerned, rapid diagnostic tests such as serum PCT (procalcitonin) and IL-1β (interleukin-1 beta) may be used as accurate markers for diagnosis of acute pyelonephritis (Pecile et al., 2004; Gürgöze et al., 2005). PCT is a peptide precursor of the hormone calcitonin. It is composed of 116 amino acids and is produced by parafollicular cells of the thyroid and by the neuroendocrine cells of the lung and the intestine. Researchers believe that PCT rises in a response to a proinflammatory stimulus, especially of bacterial origin (Dandona et al., 1994; Bressan et al., 2009). Interleukin-1 beta is a pro-inflammatory cytokine that is vital for host-defense responses. It is secreted by a variety of cells especially monocytes and macrophages. This cytokine is an important mediator of the inflammatory response, and is involved in a variety of cellular activities including cell proliferation and apoptosis (Lopez-Castejon and Brough, 2011). Although, many researchers believe that these rapid diagnostic tests are valuable markers for diagnosis of acute pyelonephritis (Pecile et al., 2004; Gürgöze et al., 2005; Bressan et al., 2009) but some other disagree (Tuerlinckx et al., 2005; Güven et al., 2006). Based on this controversy, the present study was conducted to determine the diagnostic value of PCT and IL-1β in children with acute pyelonephritis.

Material and Methods

In this prospective cross-sectional study 79 children with a first episode of proven UTI were investigated. This study was conducted in the Qazvin Children

Hospital affiliated to the Qazvin University of Medical Sciences in Qazvin, Iran in 2012. This hospital is the only children's teaching and referral hospital in Qazvin Province. Children that met the following criteria were selected for the study (inclusion criteria): (1) first episode, (2) presence of clinical signs and symptoms such as fever, abdominal pain, dysuria, anorexia and nausea, (3) pyuria, (4) positive urine culture (any growth of a single bacterial pathogen from suprapubic aspiration or $>10^4$ colony-forming units (CFUs)/ml from a catheterized specimen or $>10^5$ CFUs/ml in samples collected by midstream clean-void urine or urine bags. In patients with positive urine bag samples, UTI was confirmed only when the first and the second confirmatory bag samples were positive) (Hansson and Jodal, 2004; Gürgöze et al., 2005). Patients who had received antibiotics therapy or had concomitant disease were excluded from the study (exclusion criteria). The age of patients was between 1 month and 12 years. Sample size was calculated based on the following parameters: P=65%, $\alpha = 0.05$, $1-\alpha = 0.95$, $d = 0.13$, $\beta = 0.2$, $1-\beta = 0.8$ (Gürgöze et al., 2005). Consecutive sampling continued until the desired sample size was reached. All blood samples were taken before antibiotic therapy. WBC count, neutrophil count, ESR, and CRP concentration were measured as soon as possible. For measuring serum PCT and IL-1β, 4 ml of blood was taken from peripheral vein and then, the serum was obtained by centrifugation at 3,000 rpm for 5 minutes at 4 °C. The serum was then poured into acid-washed tubes and frozen –20 °C prior to analysis in order to measure PCT and IL-1β levels. The serum C-reactive protein concentration was determined by rapid immunometric methods (quantitative test kit for CRP, Parsazmun Co., Tehran, Iran) and erythrocyte sedimentation rate was measured by Westergren method (Lewis et al., 2001). The serum PCT was determined by using an electrochemiluminescence immunoassay (ECLIA) (Elecsys Brahms PCT kit, Roche, Germany). In addition IL-1β was measured by an enzyme-linked immunosorbent assay (Human IL-1beta Platinium ELISA kit, eBioscience, Austria). In all patients DMSA renal scintigraphy was performed within 7 days following admission. Based on the DMSA renal scan (gold standard) result, the patients were divided into acute pyelonephritis (n=33) and lower UTI (n=46) groups. In DMSA renal scan, the acute pyelonephritis was diagnosed upon observation of focal or diffuse areas of diminished uptake that are associated with preservation (or at times even bulging) of renal cortical outline (Hansson and Jodal, 2004). The two groups were compared with each other regarding variables such as age, sex, and laboratory and imaging findings. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum PCT and IL-1β were determined and compared with other inflammatory markers such as fever, WBC count, neutrophil count, ESR, and CRP. Variables of the two groups were compared with each other using chi-square test, *t*-test, and Mann-Whitney test. The data were analyzed using SPSS software (version 15). P-value less than 0.05 was considered significant.

Ethics

This study was approved by ethics committee of the Research Department of the Qazvin University of Medical Sciences (Project No. 260). All parents were provided information regarding the research method in simple language. The children were included in the study after their parents agreed and signed the informed consent form.

Results

Out of 79 children affected with UTI 33 patients had acute pyelonephritis and 46 lower UTI. The acute pyelonephritis group included 2 males and 31 females. These values in lower UTI group were 3 males and 43 females, respectively (P=0.934). Minimum and maximum age of the patients in pyelonephritis group was 5 months and 12 years with median of 3 years, respectively. These values in lower UTI group were 1 month and 10 years with median of 1.08 years, respectively (P=0.061). There was no significant difference between the two groups regarding sex and age (P>0.05). The most common clinical signs and symptoms in all patients were fever and anorexia. *Escherichia coli* was the most common organism responsible for UTI in the two groups (P=0.633). The values of WBC count, neutrophil count, ESR and serum concentrations of CRP, procalcitonin and IL-1β were greater in

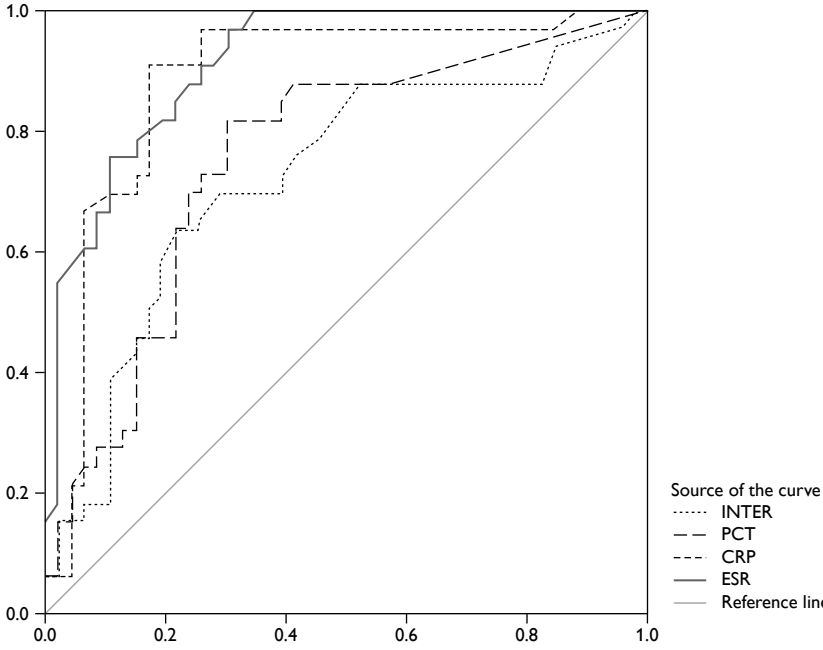

Figure 1 – Receiver operating characteristic (ROC) curve for specificity and sensitivity of ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), PCT (procalcitonin) and IL-1β (interleukin-1 beta) measurements.

acute pyelonephritis group than lower UTI group (P<0.05) (Table 1). Sensitivity, specificity, PPV, and NPV of inflammatory markers were determined with different cut-point values (Table 2). The median area under the ROC curve was 0.914 for ESR (95% confidence interval [CI] 0.855–0.974, P=0.001) and 0.883 for CRP (95%

Table 1 – Comparison of laboratory findings between acute pyelonephritis and lower UTI groups

Laboratory findings	Acute pyelonephritis (n=33)	Lower UTI (n=46)	P-value
WBC count (/mm^3)	14,600 (6,900–25,600)	9,400 (3,900–11,200)	0.001
neutrophil count (/mm^3)	71 (27–92)	45.5 (10–85)	0.001
ESR (mm/h)	64 (16–128)	11 (2–95)	0.001
CRP (mg/dl)	51.9 (0.2–115)	2 (1–98)	0.001
procalcitonin (ng/ml)	0.245 (0.2–77.6)	0.026 (0.02–7.79)	0.001
IL-1β (pg/ml)	4 (0.8–259)	1.65 (0.7–83.3)	0.001

UTI – urinary tract infection; WBC – white blood cell; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; IL-1β – interleukin-1 beta; values are presented as median (range) (Mann-Whitney test)

Table 2 – Sensitivity, specificity, PPV and NPV of inflammatory markers with different cut-point values

Inflammatory markers (cut-point value)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall agreement	Kappa	P-value
neutrophil count (50%)	84.8	54.3	57.1	83.3	67.0	0.367	<0.001
neutrophil count (60%)	69.0	72.0	63.9	76.7	71.0	0.409	<0.001
WBC (10,000/mm^3)	81.8	54.3	56.2	80.6	65.8	0.340	0.001
WBC (12,000/mm^3)	73.0	67.3	61.5	77.5	70.0	0.391	<0.001
WBC (15,000/mm^3)	48.0	90.0	76.2	70.6	72.1	0.397	<0.001
ESR (10 mm/h)	100.0	48.0	58.0	100.0	70.0	0.430	<0.001
ESR (20 mm/h)	94.0	70.0	69.0	94.0	79.7	0.604	<0.001
ESR (30 mm/h)	84.0	79.0	74.0	88.0	81.0	0.618	<0.001
ESR (40 mm/h)	76.0	85.0	78.0	83.0	81.0	0.608	<0.001
CRP (6 mg/dl)	97.0	67.0	68.0	96.0	79.7	0.607	<0.001
CRP (10 mg/dl)	97.0	74.0	73.0	97.0	83.5	0.677	<0.001
CRP (20 mg/dl)	85.0	83.0	77.7	88.3	83.5	0.666	<0.001
PCT (0.4 ng/ml)	31.0	84.7	58.8	63.0	62.0	0.162	0.108
PCT (0.5 ng/ml)	31.0	84.7	58.8	63.0	62.0	0.162	0.108
PCT (0.6 ng/ml)	31.0	86.9	62.5	63.4	63.2	0.186	0.060
IL-1β (5 pg/ml)	39.3	89.1	72.2	67.2	68.3	0.305	0.003
IL-1β (6.9 pg/ml)	27.2	90.0	64.3	63.0	63.2	0.179	0.060
IL-1β (10 pg/ml)	21.2	90.0	58.3	61.1	60.7	0.114	0.207
IL-1β (20 pg/ml)	15.1	93.5	62.5	60.5	60.7	0.097	0.210

PPV – positive predictive value; NPV – negative predictive value; WBC – white blood cell; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; PCT – procalcitonin; IL-1β – interleukin-1 beta

confidence interval [CI] 0.801–0.965, P=0.001), 0.756 for PCT (95% confidence interval [CI] 0.646–0.866, P=0.001), and 0.424 for IL-1β (95% confidence interval [CI] 0.607–0.841, P=0.01) (Figure 1).

Discussion

Differentiation between acute pyelonephritis and lower UTI is vital. Delay in diagnosis of acute pyelonephritis can lead to severe complications such as renal scaring, arterial hypertension and chronic renal failure. Thus, rapid identification and appropriate treatment of this type of UTI can prevent mentioned complications (Hansson and Jodal, 2004; Faust et al., 2009). To achieve this goal, it is recommended to use the diagnostic methods that are accurate, fast and convenient. Renal scintigraphy with Tc-99m dimercaptosuccinic acid (DMSA) is considered as the gold standard for the diagnosis of acute pyelonephritis in children. However, the DMSA is not readily available in all centers, exposes the patients to radiation, and also cannot distinguish between old scarring and acute parenchymal involvement (Hansson and Jodal, 2004; Gürgöze et al., 2005; Faust et al., 2009; Ifergan et al., 2012). Hence, use of biological markers that would assist the clinician predicting acute pyelonephritis would be valuable. Several studies were conducted to determine the accuracy of rapid diagnostic tests such as PCT and IL-1β (Dandona et al., 1994; Pecile et al., 2004; Gürgöze et al., 2005; Bressan et al., 2009). The results obtained in this context are contradictory (Gervaix et al., 2001; Pecile et al., 2004; Gürgöze et al., 2005; Tuerlinckx et al., 2005; Güven et al., 2006; Kotoula et al., 2009). Several studies showed that PCT and IL-1β have good diagnostic accuracy in diagnosis of acute pyelonephritis (Gervaix et al., 2001; Pecile et al., 2004; Gürgöze et al., 2005; Kotoula et al., 2009). Kotoula et al. (2009) reported that the sensitivity, specificity, and positive and negative predictive values of PCT using a cut-off value of 0.85 ng/ml were 89, 97, 96, and 91%, respectively. Authors concluded that serum PCT is a better marker than ESR, CRP, and leukocyte count for the early prediction of acute pyelonephritis in children (Kotoula et al., 2009). The study of Gervaix et al. (2001) showed that a positive PCT value predicted renal involvement in 87 to 92% of children with febrile UTI, compared with 44 to 83% using CRP values. Authors concluded that a rapid determination of procalcitonin concentration could be helpful for the treatment of children with febrile UTI (Gervaix et al., 2001). The sensitivity, specificity, positive and negative predictive values of PCT for the prediction of acute pyelonephritis in Pecile et al. (2004) study were 83.3, 93.6, 93.7 and 83%, respectively. These values were greater than those with CRP measurement (Pecile et al., 2004). Another study has shown that using a cut-off of 0.5 ng/ml for PCT, 6.9 pg/ml for IL-1β and 20 mg/l for CRP, the sensitivity and specificity in distinguishing between lower UTI and acute pyelonephritis were 58 and 76% for PCT, 97 and 59% for IL-1β, 97 and 58% for CRP, respectively. The authors concluded that both serum PCT and IL-1β levels may be used as accurate markers for diagnosis of acute pyelonephritis (Gürgöze et al., 2005). In contrast to

the above mentioned authors, other found that these rapid diagnostic tests are not valuable markers for differentiating between acute pyelonephritis and lower UTI (Tuerlinckx et al., 2005; Güven et al., 2006). Tuerlinckx et al. (2005) found lower sensitivity and specificity for serum procalcitonin (68% and 23%, respectively) with no obvious difference regarding the cut-off or the population's characteristics. And also, Güven et al. (2006) conducted a prospective study with 33 children and were unable to show a significant correlation between parenchymal damage and PCT. In our study the values of all inflammatory makers such as WBC count, neutrophil count, ESR, serum CRP, PCT and IL-1β concentrations were greater in acute pyelonephritis patients than lower UTI group. These findings were compatible with Pecile et al. (2004) and Gürgöze et al. (2005) studies. Although, the specificity of PCT and IL-1β for different cut-off values (0.4, 0.5, 0.6 ng/ml) (5, 6.9, 10, 20 pg/ml) were acceptable but the sensitivity of these markers were very low (less than 39%). These results are concordant with Tuerlinckx et al. (2005) study. In our study, ESR and CRP was superior to PCT and IL-1β as an indicator of acute pyelonephritis, because the ROC curve for specificity and sensitivity was greater for ESR and CRP than for PCT and IL-1β. According to low sensitivity of PCT and IL-1β in our study, it seems that these rapid diagnostic tests are not good quality biologic markers for differentiating between acute pyelonephritis and lower UTI. Thus, we suggest that using of conventional inflammatory markers such as ESR and CRP besides the other clinical findings can facilitate to predict acute pyelonephritis in children.

Conclusion

This study revealed that serum PCT and IL-1β are not good biologic markers for differentiating acute pyelonephritis from lower UTI. It seems that conventional inflammatory markers such as ESR and CRP besides the clinical findings are more reliable for the diagnosis of acute pyelonephritis in children.

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