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Serum Procalcitonin is an Early and Reliable Diagnostic Marker for Diagnosis of Urinary Tract Infection

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ABSTRACT: Rapid diagnosis of bloodstream infections (BSIs) in the emergency department (ED) and also before starting the antibiotic is very important. We studied the usefulness of procalcitonin as a marker of BSI in 50 patients admitted in Dhaka medical college hospital, Bangladesh. Serum samples were taken from the same patients whose urine culture were done. Procalcitonin levels were compared with urine culture results and other parameters. Procalcitonin levels of less than 0.05 ng/mL were considered negative; all other levels were considered positive. Serum PCT was done on 50 cases. Out of those cases, 43 (86.00%) were found positive by both PCT and urine culture and 3 (6.00%) cases were found negative by both PCT and urine culture. 3 (6.00%) cases were found positive only by urine culture and 1 (2.00%) case was found positive only by PCT test but negative by culture. Considering urine culture as gold standard, sensitivity of PCT was 93.48%, specificity of PCT was 75.00%, positive predictive value was 97.72% and negative predictive value was 50.00%. Although this study comprised a small number of patients, we found that Procalcitonin is a useful marker to rule out sepsis and decide upon urinary tract infection treatment.

KEYWORDS: Procalcitonin, urinary tract infection, urine culture, blood stream infection.

I. INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial infection accounting for 25% of all infections. It is one of the most important causes of morbidity and also the second most common cause of hospital visit (Ronald and Pattullo 1991). Worldwide, about 150 million people are diagnosed with urinary tract infection each year costing the global economy in excess of 6 billion dollars (Gonzalez and Schaeffer 1999). In UTI the presence of growth of more than 10^5 colony forming unit (CFU) of bacteria per ml of urine for asymptomatic individual and 10^3 for symptomatic individual (Gandhi *et al.*, 2017). C-reactive protein is an acute-phase protein produced by the liver in response to tissue injury or infection. C-reactive protein level can also be very high in nonseptic states, e.g., postoperatively and in the presence of inflammatory disease (Ludwig, Kümmel *et al.* 1998, Oberhofer, Juras *et al.* 2012).

Procalcitonin (PCT) is a 116-amino acid propeptide of calcitonin, which could be an indicator of bacterial infections. PCT has been reported to be a reliable diagnostic biomarker of bacterial infections due to its specificity, short time of induction and long half-life. Common biomarkers for UTI includes serum leukocyte or neutrophil counts, C-reactive protein (CRP) and interleukins, compared with which, PCT has been proved to be more specific in terms of differentiating acute pyelonephritis from LUTIs (Assicot, Bohuon *et al.* 1993, Zhang, Yang *et al.* 2016). PCT is also specific in terms of differentiation of viral and bacterial infections particularly in children (Simon, Gauvin *et al.* 2004, Leroy and Gervaix 2010). In addition, PCT can be detected in serum 2 hours after the infections and the PCT levels, thereafter, rises and reaches a plateau 12 hour after the infections (Zaffanello, Brugnara *et al.* 2008, Leroy and Gervaix 2010). Serum concentrations in healthy individuals are extremely low, <0.05 ng / ml, or even immeasurable (Suberviola, Castellanos-Ortega *et al.* 2012). In systemic inflammation, particularly in bacterial infections, under the influence of inflammatory cytokines and bacterial endotoxin, it is produced in a number of tissues (lung, liver, kidney, adipose tissue) and goes in circulation, when its level can increase up to 1000 times (Chan and Gu 2011). Thus, the molecule seems to be closely dependent on the cytokine response against micro-organisms, with some cytokines as early markers of bacterial invasion. High serum PCT levels appear to correlate with the severity of sepsis and may be useful in prognosis because they rapidly reflect appropriate antibiotic therapy. PCT may be a useful marker in critical situations when clinical features are missing ((Meisner 2005). PCT increases in patients with septic shock. In



viral and localized bacterial infections plasma PCT levels are lower than patients with systemic infections (Assicot, Bohuon et al. 1993), Autoimmune disease (Eberhard, Haubitz et al. 1997) and neoplastic disorders (Fleischhack, Kambeck et al. 2000) do not induce PCT. If systemic infection is present in immunosuppressed patients, PCT remains elevated (Dandona, Nix et al. 1994, Al-Nawas, Krammer et al. 1996).

The production of PCT during inflammation is linked to the bacterial endotoxin, the most potent stimulator of PCT release into circulation (Dandona, Nix et al. 1994). The administration of TNF, IL-1, IL-2 and IL-6 also leads to an increase in PCT. PCT may guide treatment decisions and reduce antibiotic administration. A serum procalcitonin concentration of 0.05 ng/ml or lower indicates the absence of bacterial infection and the use of antibiotics is strongly discouraged. Procalcitonin levels of 2 ng/ml are highly indicative of a bacterial infection and antibiotics are strongly recommended (Christ-Crain, Stolz et al. 2006).

The PCT is a reliable marker that contributes to the early diagnosis of invasive bacterial infections and evaluation of their severity and prognosis. Sequenced way of measuring PCT provides objective data which, along with clinical evaluation, form the basis on which the PCT guidelines of antibiotic therapy is based. Respectable number of randomized controlled trials confirmed that treating according to the PCT antibiotic stewardship, reduces antibiotic exposure, without compromising safety of patients and the treatment outcome. So, inclusion of PCT in diagnostic and therapeutic protocols of bacterial infections can reduce the cost of treatment and the emergence of multi-resistant strains of bacteria.

II. MATERIALS AND METHODS

A cross sectional study was done from July 2016 to June 2017 in Dhaka Medical College Hospital. Total 50 urine samples of clinically suspected UTI patients and blood samples from the same patients were collected.

UTI can readily be diagnosed by microscopical examination of urine. A standardized centrifuged urinary sediment examined under a cover slip is recommended. It is cheap and differentiation of formed elements (red and white blood cells, bacteria) is easier in thin fluid layers than in traditional glass chambers. Centrifugation always leads to loss of particles and may produce inaccurate results in quantitative terms, on the other hand in unspun samples a number of relevant elements could be missed. Thus, the results after centrifugation with a standardized procedure are more sensitive and specific. The counts are usually given per low power field or high-power field. Results could also be given per unit volume of urine. At the high magnification (40x) the presence of 1-10 microorganisms/high power field is indicative of bacteriuria the presence of ≥ 10 white blood cells/high power field is indicative of pyuria.

2 ml of urine was transferred aseptically from each sample in a sterile test tube for culture and remaining 10 ml of urine was centrifuged at 3000 rpm for five minutes to see the pus cell, RBC, epithelial cell, cast, crystal and others under microscope.

The detection of significant numbers of pathogenic bacteria from culture of the urine has remained the gold standard for the diagnosis of UTI.

From the same patients with all aseptic precaution, after disinfecting the selected veni-puncture site with 2% povidone iodine followed by 70% alcohol, 1 ml of blood was collected in a sterile microcentrifuge tube for serum procalcitonin test.

The whole blood was allowed to clot by leaving it undisturbed for 15 – 30 minutes at room temperature. Then it was centrifuged at 1000-2000xg for 10 minutes. Following centrifugation the supernatant liquid component that is serum was immediately transferred into another clean microcentrifuge tube by using pasteur pipette. Each tube was labeled with appropriate patient information and sample number.

The sample was then analyzed for procalcitonin test in the laboratory of the Department of Microbiology of DMCH. If it was not possible to do procalcitonin test immediately then serum was stored at 2-8⁰C and the test was done within 2 days of sample collection.

Other parameters were collected from the patients that have been done after hospital admission.

According to American College of Chest Physicians/ Society of Critical Care Medicine 1992,

At PCT < 0.5 ng/ml-Systemic infection/ sepsis is not likely,
 At PCT > 0.5 and < 2 ng/ml- Moderate risk for progression to severe systemic infection,
 At PCT > 2 and < 10 ng/ml- High risk for progression to severe systemic infection,
 At PCT > 10 ng/ml- High likelihood of severe sepsis or septic shock.

III. RESULTS AND DISCUSSION

Table 1: Comparison of serum PCT level with pus cell among study group (N = 50)

PCT test	Suspected UTI		
	Group A	Group B	Group C
	(Few pus cell)	(Moderate pus cell)	(Plenty pus cell)
	n(%)	n(%)	n(%)
Negative	2(28.57)	1 (5.26)	0 (0.00)
Weakly positive	2 (28.57)	6 (31.57)	4 (16.66)
Moderately positive	3 (42.85)	5 (26.31)	7 (29.16)
Strongly positive	0 (0.00)	3 (20.00)	7 (29.16)
Total	7 (100.00)	19 (100.00)	24(100.00)

N = total number of PCT

n = number of Group A, Group B, Group C

Note: Negative PCT test = PCT level <0.1 ng/ml

Weakly positive PCT test = PCT level 0.1-0.25 ng/ml

Positive PCT test = PCT level >0.25-0.50 ng/ml

Strongly positive PCT test = PCT level >0.50 ng/ml

Table 1 shows that the comparison of serum PCT level among study groups. Out of 7 few pus cell present cases 3 (42.85%) showed moderately positive, 2 (28.57%) showed weakly positive and 2 (28.57%) showed negative PCT test. Out of 19 moderately pus cell present case 3 (20%) revealed strongly positive test, 5 (26.31%) revealed moderately positive, 6 (31.57%) revealed weakly positive and 1 (5.26%) revealed negative PCT test. There were 7 (29.16%) strongly positive, 7 (29.16%) moderately positive and 4 (16.66%) weakly positive PCT test among 24 plenty pus cell present cases and no negative PCT test was found in this group.

Table 2: Comparison of serum PCT level with urine culture results (N=50)

Serum PCT	Urine culture		Total n (%)
	Positive n (%)	Negative n (%)	
Positive	43 (86.00)	1 (2.00)	44 (94.00)
Negative	3 (6.00)	3 (6.00)	6 (6.00)
Total	46 (92.00)	4 (8.00)	50 (100.00)

N= Total number of PCT



n= Number of positive and negative cases of PCT and culture

Table 2 shows that serum PCT was done on 50 cases. Out of those cases, 43 (86.00%) were found positive by both PCT and urine culture and 3 (6.00%) cases were found negative by both PCT and urine culture. 3 (6.00%) cases were found positive only by urine culture and 1 (2.00%) case was found positive only by PCT test but negative by culture.

Table 3: Characteristics associated with the procalcitonin measurement for prediction of urinary tract infection

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PCT 93.48	75.00	97.72	50.00

PPV= Positive predictive value

NPV= Negative predictive value

Table 3 shows that, considering urine culture as gold standard, sensitivity of PCT was 93.48%, specificity of PCT was 75.00%, positive predictive value was 97.72% and negative predictive value was 50.00%.

Table 4: Distribution of UTI cases according to the level of PCT

PCT level (ng/ml)	Number of patients	Bacterial infection
< 0.1	6 (12.00%)	Very unlikely
0.1 - 0.25	4 (8.00%)	Unlikely
>0.25 - 0.50	5 (10.00%)	Likely
> 0.5	35 (70.00%)	Very likely

Table 4 shows the distribution of UTI cases according to the level of PCT. Out of 50 patients 6 (12.00%) were found < 0.1 ng/ml who seems to have bacterial infection very unlikely, 4 (8.00%) were found 0.1 – 0.25 ng/ml who also seems to have bacterial infection unlikely, 5 (10%) were found >0.25 – 0.5 ng/ml who had bacterial infection likely and 35 (70%) were found >0.5 ng/ml who had bacterial infection very likely.

Table 5: Laboratory data of other parameters

	Non obstructed UTI (median)	Obstructed UTI (median)	P value
PCT (mg/dl)	1.67	34.28	<0.0001
CRP (mg/dl)	8.9	12.42	Not significant
Creatinine (mg/dl)	1.2	2.45	<0.0001
Leukocyte count (/μl)	11237.5	15432.37	<0.05
Platelet(/μl)	23.24	18.97	Not significant

Table 5 shows that laboratory data of 50 patients of non-obstructed UTI (median) and obstructed UTI (median) show that p value was significantly higher in creatinine and procalcitonin level. White blood cells showed significant difference (<0.05), and platelet count and C-reactive protein did not differ significantly.



IV. DISCUSSION

UTI is a disease commonly encountered in the clinical setting. Sepsis resulting from UTI is a serious life-threatening condition. It has been reported that the mortality rate due to urosepsis is 16.1%. In addition, it has been reported that 78% of urosepsis is due to urinary tract obstruction.

C-reactive protein is generally regarded as a useful marker for the diagnosis of sepsis and is used along with blood culture. However, these methods are rarely adequate for diagnosing sepsis and a test permitting more rapid and efficient diagnosis has long been necessary

In this study, procalcitonin has been used as early marker for the diagnosis of CAUTI using urine culture as gold standard. This study also evaluated the bacterial isolates of catheter associated urinary tract infection and their antimicrobial resistance pattern.

In recent years, measurement of procalcitonin and other inflammatory mediators have been reported as a sensitive parameter for the early diagnosis of bacterial infection and evaluating its outcome (Zaffanello, Brugnara et al. 2008). Proinflammatory cytokines play a role in the pathogenesis of bacterial infections. Production of these cytokines seems to trigger procalcitonin secretion from target cells.

PCT is a propeptide of calcitonin with 16 amino acids and devoid of hormonal activities, was initially described to have the potential of being a marker of bacterial infection (Hatherill, Tibby et al. 1999, Gervaix, Galetto-Lacour et al. 2001). PCT increases in blood 6 hours after a stimulus, reaches a plateau between 12-48 hours and then decreases if the stimulus stops. In this study, among 46 culture positive UTI cases, PCT was found positive in 43 (86%) cases (Table 2). (Ayazi, MAHYAR et al. 2009) found 70.6% positive PCT in culture positive cases. Benadaret al. (1998) and pecileet al. (2004) found 83.3% and 94.4% positive PCT respectively whose urine were culture positive. Different published data indicate that a highly significant correlation is present between elevated PCT level and severity of renal involvement and subsequent sequele (Benador, Siegrist et al. 1998, Ayazi, MAHYAR et al. 2009). (Riedel, Melendez et al. 2011) found in their study, in 16 patients, there was evidence of Rapid diagnosis of infections by culture, and 12 (75%) of 16 patients had a procalcitonin level of more than 0.1 ng/mL. In 186 (63.1%) of 295 samples, procalcitonin values were less than 0.1 ng/mL, and all were culture negative.

PCT has some advantages other biomarkers in common clinical use such as C-reactive protein (CRP) and white blood cell count. The advantages of PCT over older markers include, specificity for bacterial infection (verses inflammation in general), the rapidity of its rise after a severity of illness (higher levels in more severely ill), and the lack of impact of anti-inflammatory and immunosuppressive states on production (Das, Barua et al. 2016). In the present study, at a cut-off value of 0.5 ng/ml, the sensitivity and specificity of PCT were found to be 93.48% and 75% respectively, the positive predictive value was 97.72% and negative predictive value was 50% compared with urine culture (Table 3). (Kumar, Jalan et al. 2017) found 92.6% sensitivity, 80.3% specificity of serum procalcitonin which correlate with this study. (Steinmann, Kaase et al. 2011) found Procalcitonin level of less than 0.1 ng/mL were considered negative; all other levels were considered positive. In 16 patients, there was evidence of culture, and 12 (75%) of 16 patients had a procalcitonin level of more than 0.1 ng/ml. In 186 (63.1%) of 295 samples, procalcitonin values were less than 0.1 ng/mL, and all were culture negative. With a calculated threshold of 0.1475 ng/mL for procalcitonin, sensitivity and specificity for the procalcitonin assay were 75% and 79%, respectively. The positive predictive value was 17% and the negative predictive value was 98%. Melendez et al. (2011) (Sharma, Pathak et al. 2013) found : sensitivity 75%; specificity 78.9%; Similarly, (Kumar, Jalan et al. 2017) found, 87% sensitivity, 63.4% specificity in their study.

Among the 46 urine culture positive cases, an elevated PCT level was noted in 44 (94%) case (Table 4), 8% had PCT level between 0.1-0.25 ng/ml, 10% had PCT level between 0.26 – 0.50 ng/ml, 35% had PCT level >5 ng/ml (Table 2). Similarly, (Sucilathangam, Amuthavallik et al. 2012) reported elevated serum PCT level in 92.85% cases. Since the serum PCT levels were elevated in almost all the culture proven sepsis cases, PCT can be used as a good tool for the diagnosis of the sepsis on the day of the admission, before the culture report is available which needs usually 3-5 days. (Sandkovsky, Kalil et al. 2015, Uslan 2016) described the impact of PCT levels on antibiotic prescription. They suggested, if PCT value <0.1 ng/ml, bacterial infection is very unlikely and cessation of antibiotic is strongly encouraged, if PCT value 0.1-0.25 ng/ml, bacterial infection is unlikely and cessation of antibiotic is encouraged, if PCT value >0.25-0.50 ng/ml, bacterial infection is likely and antibiotic use is recommended, if PCT value >0.5 ng/ml, bacterial infection is very likely and antibiotic use is strongly recommended. In this study, 12% patient had PCT level <0.1, 8% patient had PCT level 0.1-0.25, 10% patient had PCT level >0.25-0.05, 70% patient had PCT level >0.5



(Table 4.8). PCT should be placed into the clinical context of each patient scenario considering the site of possible infection, the likelihood of bacterial infection, the severity of illness, and any other pertinent clinical data.

If procalcitonin level is high, it is important tool diagnosis of sepsis when compared with C-reactive protein (Uzzan, Cohen et al. 2006, Tang, Eslick et al. 2007). In a study comparing PCT with CRP, the diagnostic sensitivity was 77%, specificity was 79%(Wacker, Prkno et al. 2013). Although our study contained a very small number of populations, our results were similar to other study.

V. CONCLUSION

PCT is not only a useful marker to rule out bacteremia but also can predict severe bacteremia. The procalcitonin level could be used as a potential biomarker for the clinician to make a rapid decision to start empirical antibiotic therapy and to avoid unnecessary antibiotic therapy in suspected UTI cases.

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