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Original research article

Procalcitonin Serum Levels in Urinary Tract Infection in Children below 5 years of age: A case-control study

Dr. Shyam Bahadur Prasad[1], Dr. Amresh Kumar Sahu[2], Dr. Arvind Kumar[3]

[1]Senior Resident, Department of Paediatrics, Government Medical College and Hospital, Bettiah, West Champaran, Bihar, India.

[2]Senior Resident, Department of Paediatrics, Government Medical College and Hospital, Bettiah, West Champaran, Bihar, India.

[3]Professor and HOD, Department of Paediatrics, Government Medical College, Bettiah, West Champaran, Bihar, India.

Corresponding Author: Dr. Amresh Kumar Sahu

Abstract

Aim: The aim of the present study is to evaluate the Procalcitonin Serum Levels inChildren Younger than Five Years Old with Urinary Tract Infection.

Methods: This case-control study was done in the Department of Paediatrics, Government Medical College, Bettiah, West Champaran, Bihar, India from January 2019 to November 2019, The 100 (50 cases and 50 controls) children less than 5 years of age were included in this study. The children in the case group suffered from UTI based on a positive urinary culture test. They also were undergone VCUG and accordingly were divided into two groups: having VUR and not having VUR. Their serum levels of PCT weremeasured before starting antibiotic therapy usingthe chemiluminiscence immunoassay (CLIA).They (The control group),had negativeresults for both urine culture (UTI) and urinary analysis tests and the serum levels of PCT were measured for them. In both groups children under 5 years without any genetic diseases and chronic kidney disease, were included in the study.

Results: Of the samples, 70 childrens (70%) were female. The median age of the samples was 22.5 months with an interquartile range between 10.5 and 35.5 months. Although, 70% of them had no vesicoureteral reflux, 20% and 10% of the samples suffered from severe unilateral VUR and sever bilateral vesicoureteral reflux, respectively. The VCUG and the serum status of PCT were compared between the groups. Accordingly, both the evaluation methods diagnosed 40 children to be healthy, while 90% of children with VUR positive simultaneously were PCT positive. The odds of one positive and two positive for one way 1.875 (P=0.011) times and 1.126(P=0.873) times were higher than the group without reflux. However the odds of 4 positive for one way 0.289 (P=0.2) times was lower than control group. Considering the number of cases, we rely only on descriptive statistics for other groups. According to our findings, 60% of the samples were positive with regard to the level of serum PCT. One-half of those samples (32 people) who was diagnosed to be healthy using VCUG had a normal level of serum PCT. The kappa score for the level of serum PCT was 0.2 ($P < 0.0001$).

Conclusion: No significant relationship exists between vesicoureteral reflux and the serum level of PCT.

Keywords: PCT, VCUG, UTI

Introduction

Serious bacterial infections (SBI) can be difficult to distinguish from many self-limiting benign viral infections affecting children, especially during the prodrome. When the diagnosis is unclear, clinicians may use biomarkers, such as C-reactive protein (CRP) and procalcitonin (PCT), to aid clinical decision-making.[1] Procalcitonin is the precursor for calcitonin and is produced by parafollicular cells.[2,3] It is a 116-amino acid protein that has roles in calcium metabolism.[4] PCT is elevated during infection and typically rises within two hours of the onset of a bacterial infection reaching a peak at 24 to 36 hours.[4] Procalcitonin levels are attenuated by the presence of interferon gamma that is typically released during viral infections leading to suggestions that PCT may have uses in distinguishing viral from bacterial infections.[4] The existing literature regarding the test accuracy of PCT in children is favourable with at least five meta-analyses demonstrating that PCT is accurate when used to diagnosis SBI across a range of paediatric settings.[5-9] The two most commonly used PCT cut-offs are 0.5 ng/ml and 2.0 ng/ml.[5-9] The lower cut-off of 0.5 ng/ml typically provides an approximate 80% sensitivity for the identification of SBI whereas the higher cut-off of 2.0 ng/ml typically provides a specificity of around 90%.[5-9] Two of the five meta-analyses compared PCT to CRP with both studies reporting that PCT was more accurate than CRP for the diagnosis of SBI in children.[8,9] PCT has also been shown to be particularly useful in the assessment of febrile young infants under 90 days of age.[10-12] As technology evolves, there is increasing interest in the use of point-of-care (POC) biomarkers for the early recognition of SBI. There have been a number of studies exploring the use of POC CRP testing to identify SBI at presentation to healthcare.[13,14] These studies have reported that the use of POC CRP can help to risk stratify children at triage/initial assessment.[13] Procalcitonin testing may however, represent the ideal POC test for detecting SBI in children due to its greater test accuracy.

Material and Methods

This case-control study was done at the Department of Paediatrics, Government Medical College, Bettiah, West Champaran, Bihar, India from January 2019 to November 2019, after taking the approval of the protocol review committee and institutional ethics committee.The 100 (50 case and 50 control) children less than 5 years of age were included in this study. The children in the case group suffered from UTI based on a positive urinary culture test. They also were undergone VCUG and accordingly were divided into two groups: having VUR and not having VUR. Their serum levels of PCT were measured before starting antibiotic therapy using the chemiluminiscence immunoassay (CLIA).Those in the control group were UTI negative children that referred to the same healthcare setting for routine vaccination. They had negative results for both urine culture (UTI) and urinary analysis tests that the serum levels of PCT were measured for them. In both groups children under 5 years without genetic diseases and chronic kidney disease included in the study. Data collection tools were conducted based on a researcher-made questionnaire consisting of demographic questions, and questions regarding the laboratory and imaging results.

Statistical analysis

The data was analyzed via the SPSS software for windows.The descriptive and inferential statistics used in this study were percentage, independent t-test, Chi-squared test, and Roc curve.

Results

Of the samples, 70 children (70%) were female. The median age of the samples was 22.5 months with an interquartile range between 10.5 and 35.5 months. Although, 70% of them had no vesicoureteral reflux, 20% and 10% of the samples suffered from severe unilateral VUR and severe bilateral vesicoureteral reflux, respectively. The VCUG and the serum status of PCT

were compared between the groups. Accordingly, both the evaluation methods diagnosed 40 children to be healthy, while 90% of children with VUR positive simultaneously were PCT positive. The odds of one positive and two positive for one way 1.875 (P=0.011) times and 1.126(P=0.873) times were higher than the group without reflux. However the odds of 4 positive for one way 0.289 (P=0.2) times was lower than control group. Considering the number of cases, we rely only on descriptive statistics for other groups. According to our findings, 60% of the samples were positive with regard to the level of serum PCT. One-half of those samples (32 people) who was diagnosed to be healthy using VCUG had a normal level of serum PCT. However, 20 people of the samples diagnosed to be healthy using voiding cystourethrogram had a positive result of level of serum PCT. The positive and negative predictive values of the serum level of PCT were 42% and 88%, respectively. In this respect, 48% of the samples diagnosed by serum level of PCT were false positive and 10% were false negative. It meant that sensitivity and specificity of PCT measurement were 88% and 48%, respectively. Globally, the odds of negative VUR were 8 times higher than positive VUR. In addition, the odds of negative VUR were 28 times and 3.74 times higher than positive VUR in males and females, respectively.

The kappa score for the level of serum PCT was 0.2 (P < 0.0001) (Table 2). Accordingly, the sensitivity of the level of serum PCT for the female samples was 80% and for male samples were 100%. Additionally, the specificity of the serum PCT for the female and male samples was 40% and 66%, respectively. The positive predictive value of serum PCT for the female and male samples was 40% and 52% respectively (Table 3).

Table 1: The frequency of the diagnosis of VUR based on the evaluation method

Group	VCUG	Procalcitonin		Kappa	Odds **ratio**	p-value
		Control N (%)	**Case N (%)**			
Total	Control=50	30 (60)	20(40)	0.3	7.5	<0.0001
	Case=50	16 (32)	34 (68)			
Boy	Control	15 (71.43)	6 (28.57)	0.51	27	0.003
	Case	(0)	4 (100)			
Girl	Control	15 (42.86)	20 (57.14)	0.196	3.67	0.028
	Case	10 (25)	30 (75)			

Table 2: The frequency of the diagnosis of VUR based on gender

Gender		**Value**		**Approx. T[b]**	**Approx. sig.**
Girl	Measure of Agreement	Kappa	.188	2.32	.032
	N of Valid Cases		75		
Boy	Measure of Agreement	Kappa	.523	2.89	.002
	N of Valid Cases		25		
Total	Measure of Agreement	Kappa	.287	3.53	.001
	N of Valid Cases		100		

Table 3: The frequency of the diagnosis of VUR based on the evaluation method and gender

VCUG * Procalcitonin* gender Cross tabulation

Gender				**Procalcitonin**		**Total Healthy**
Female	**VCUG**	**Healthy** Count % within VCUG		18_a 36%	32_b 64%	50 100%
		% within Procalcitonin		80%	56%	66%
		Ill	Count	5_a	20_b	25
			% within VCUG	20%	80%	100%
			% within Procalcitonin	18%	44%	36%
	Total		Count	23	52	75
			% within VCUG	30.67%	69.33%	100.0%
			% within Procalcitonin	100%	100%	100%
Male	**VCUG**	**Healthy**	Count	14_a	7_b	21
			% within VCUG	66.67%	33.33%	100%
			% within Procalcitonin	100%	48%	74%
		Ill	Count	0_a	4_b	4
			% within VCUG	0.0%	100%	100%
			% within Procalcitonin	0.0%	48%	22%
	Total		Count	14	11	25
			% within VCUG	56%	44%	100%
			% within Procalcitonin	100%	100%	100%
Total	**VCUG**	**Healthy**	Count	35_a	40_b	75
			% within VCUG	46.67%	53.33%	100.0%
			% within Procalcitonin	90%	54%	75%
		ill	Count	4_a	21_b	25
			% within VCUG	16%	84%	100.0%
			% within Procalcitonin	10%	42%	30%
	Total		Count	39	61	100
			% within VCUG	39%	61%	100%
			% within Procalcitonin	100 %	100%	100%

Discussion

The measurement of serum level of PCT as a biomarker using a non-invasive method is recognized for an early detection of UTI and VUR.[15-24] PCT has been demonstrated to be correlated to both acute pyelonephritis and late renal scars and predict VUR in children with UTI. [17] In our study, 75 children (75%) were female. The median age of the samples was 22.5 months with an interquartile range between 10.5 and 35.5 months. Although, 70% of them had no vesicoureteral reflux, 20% and 10% of the samples suffered from severe unilateral vesicoureteral reflux and severe bilateral vesicoureteral reflux, respectively. In other two studies, VUR was found in 26% and 11% ofchildren respectively.[19] The serum level of PCT more than 0.5 ng / ml is considered abnormal and may indicate sepsis.[15]Daily measurements of PCT can determine the adequacy and duration of antibiotic therapy as

well as the patient's prognosis. This is specifically important in the early stages of sepsis requiring empiric antibiotic therapy.[15] According to our findings, 60% of the samples were positive with regard to the level of serum PCT. One-half of those samples (40 people) who was diagnosed to be healthy using voiding cystourethrogram had a normal level of serum PCT. However, 32 patients of the samples diagnosed to be healthy using VCUG had a positive result of increased serum PCT.

In other study, only median PCT was significantly higher in patients with renal scar.[22] This study revealed no significant differences in PCT values in children with and in those without VUR and VUR grade.[22] In other study, a meaningful relationship between VUR grade more than 3 and the clinical decision regulation was not found.[19] In children with VUR grade ≥3, PCT is remarkably higher than in children with no or low-grade VUR.[17] The association of PCT with VUR in children with febrile UTI remains controversial. The positive and negative predictive values of the serum level of PCT were 42% and 88%, respectively. In this respect, 48% of the samples diagnosed by serum level of PCT were false positive and 10% were false negative. It meant that sensitivity and specificity of PCT measurement were 88% and 48%, respectively. In other study, it has been reported that PCT is a suitable predictor of cystographic findings and can be substituted with VCUG in some cases of young children with febrile urinary tract infections.[21] The positive predictive value of serum PCT for the female and male samples was 40% and 52% respectively. Now a days, the evaluation of vesicoureteral reflux is carried out using different imaging methods such as sonography, voiding cystourethrogram (VCUG), and direct radionuclide cystography (DRNC) that are accompanied with different limitations. Pediatricians are looking for other evaluation methods that are feasible, easy to implement and carries the least amount of danger to the patient In this respect, the evaluation of vesicoureteral reflux by using the serum level of PCT as a non- radiological method is suggested. However, one of the limitations of our study was the low number of our cases, that limits the widespread use of serum level of PCT in the diagnosis of pediatric UTI and VUR.

Conclusion

In conclusion, there was no statistically significant relationship between vesicoureteral reflux and the serum level of PCT. However, due to some limitations in our study, more studies are recommended with more numbers for better determination of diagnostic values of procalcitonin serum levels in relation to VUR.

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