



Evaluation of Procalcitonin Serum Levels in Children Younger than Five Years Old with Urinary Tract Infection

Mohsen Akhavan Sepahi^{1,2}, Mohammad Kazem Moslemi^{3*}
and Mohammad Reza Haeri⁴

¹Department of Pediatric Nephrology, Qom University of Medical Sciences, Qom, Iran.

²Pediatric Clinical Research of Development Center, Hazrat- Masoomeh Hospital, Qom University of Medical Sciences, Qom, Iran.

³Department of Urology, Kamkar Hospital, Qom University of Medical Sciences, Qom, Iran.

⁴Department of Clinical Biochemistry, Qom University of Medical Sciences, Qom, Iran.

Authors' contributions

This work was carried out in collaboration among all authors. Author MAS designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author MKM is the Corresponding Author and managed the analyses of the study. Author MRH managed the literature searches. All authors read and approve the final manuscript.

Article Information

DOI: 10.9734/AJPR/2020/v4i430158

Editor(s):

(1) Dr. Kanwal Preet Kaur Gill, Sri Guru Ram Das Institute of Medical Sciences & Research, Amritsar, India.

Reviewers:

(1) Simona Mihai, Victor Babes National Institute of Pathology, Romania.

(2) Mukesh Chandra Arya, S. P. Medical college, India.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/61185>

Original Research Article

Received 02 September 2020
Accepted 07 November 2020
Published 05 December 2020

ABSTRACT

Background: Children with vesicoureteral reflux (VUR) are posed to the danger of recurrent pyelonephritis, kidney scar and renal failure. Nowadays, the evaluation of VUR is carried out using different imaging methods that are accompanied with different limitations. Pediatricians usually look for other evaluation methods that are feasible, easy to implement and carries the least amount of danger to the patient.

Objectives: The aim of this study was to investigate the level of serum Procalcitonin (PCT) as a predictor of VUR instead of the voiding cystourethrogram (VCUG).

Methods: This case-control study was conducted from 2013 to 2014. One hundred and ten children younger than five years old were divided into two groups: (i) the case group with 76

*Corresponding author: Email: moslemi_urologist@yahoo.com, mkmoslemi@gmail.com;

children diagnosed with urinary tract infection (UTI) using urine culture test, and (ii) the control group with 34 healthy children. Serum levels of PCT were measured by a commercial kit. Demographic data were collected using a questionnaire and analyzed by software SPSS.

Results: Of the samples, 69.1% of them had no VUR, 20% and 10.9% of the samples suffered from severe unilateral VUR and severe bilateral VUR, respectively. With regard to the level of serum PCT, 61.8% of the samples were positive. One-half of those samples (38 people) who was diagnosed to be healthy had a normal level of serum PCT. However, 30 people (88.2%) of the samples diagnosed to be healthy using VCUG had increased level of serum PCT. The positive and negative predictive values of the level of serum PCT were 44% and 90%, respectively. In this respect, 50% of the samples diagnosed by using level of serum PCT were false positive and 11.8% were false negative. The kappa score for the level of serum PCT was 0.3 ($P < 0.0001$). The positive predictive value of the serum level of PCT for the female and male samples were 43% and 50% respectively.

Conclusions: There was no statistically significant relationship between VUR and the serum level of PCT.

Keywords: Children; urinary tract infection; procalcitonin (PCT); vesicoureteral reflux (VUR).

1. BACKGROUND

Vesicoureteral reflux (VUR) is defined as retrograde urine flow from the bladder into the upper tract and kidney that occurs secondary to a dysfunctional vesicoureteral junction [1,2]. VUR is the most common congenital urinary tract abnormality in children that usually presents with urinary tract infection (UTI) [2]. It is conventionally diagnosed and followed by voiding cystourethrogram (VCUG) that classifies the disease into five grades (I to V) [3-6].

Children with VUR are in the danger of frequent pyelonephritis that may lead to the development of kidney scare and progressive kidney dysfunction [5-8]. When associated with intrarenal reflux, it decreases the renal function, and increases UTI incidence [4,5]. VUR may also resolve spontaneously [3], but complications may occur even after resolution of VUR [6,7].

Nowadays, the evaluation of VUR is carried out using different methods that are accompanied with different limitations including lack of sufficient sensitivity and implement difficulty [1,4]. Therefore, there is a need for a new feasible vesicoureteral reflux evaluation method with the least difficulty.

PCT is the most reliable parameter for the diagnosis and differentiation between bacterial and viral infections. Therefore, an early detection of this indicator helps with appropriate and fast therapeutic intervention [9]. The main biological role of PCT is largely unknown; however, recent surveys demonstrate the role of PCT in sepsis [9,10]. The serum level of PCT more than 0.5

ng/ml is considered abnormal and may indicate sepsis. PCT compared with CRP has a higher sensitivity and specificity for the detection of bacterial induced inflammation as occurring in UTI or urosepsis [10-12].

Daily measurements of PCT can determine the adequacy and duration of antibiotic therapy. This is specifically important in the early stages of sepsis requiring empiric antibiotic therapy [12,13]. The measurement of serum PCT levels as an acute phase reactant is advised for an early detection of UTI and VUR [13-21]. Recent studies on PCT have shown its advantage over CRP and CBC in the early detection of UTI [20, 21].

2. OBJECTIVES

Given the importance of early diagnosis and treatment of UTI and vesicoureteral and VUR as the risk factor for the development of irreversible kidney damage, the aim of this study is to investigate the level of serum PCT as a predictor of vesicoureteral reflux instead of the VCUG.

3. METHODS

3.1 Design and Sample

This case-control study was conducted since January 2013 till the end of 2014. The 110 (76 case and 34 control) children less than 5 years of age who in this period referred to child care center of Qom university of medical sciences, selected using categorical sampling method. The case group selected from children with UTI positive that hospitalized in this center. 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 chemiluminescence 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 genetically diseases and chronic kidney disease included in the study.

According to the findings of some previous study and given the sensitivity ($P_1 = 37.5\%$) and specificity ($P_2 = 69\%$) of the evaluation tests for VUR, and using the following formula, 36 people in each groups were determined.

$$n = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2}$$

Therefore, the number of samples in the case and control groups was determined 76 and 34 people, respectively.

3.2 Data Collection and Analysis

Data collection tools were conducted based on a researcher-made questionnaire consisting of demographic questions, and questions regarding

the laboratory and imaging results. 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.

4. RESULTS

Of the samples, 78 children (75.7%) were female. The median age of the samples was 21 months with an interquartile range between 10 and 36 months. Although, 69.1% of them had no vesicoureteral reflux, 20% and 10.9% of the samples suffered from severe unilateral VUR and sever bilateral vesicoureteral reflux, respectively (Fig. 1). The VCUG and the serum status of PCT were compared between the groups. Accordingly, both the evaluation methods diagnosed 38 children to be healthy, while 88.2% of children with VUR positive simultaneously were PCT positive (Table 1).

The odds of one positive and two positive for one way 1.902 ($P=0.015$) times and 1.053 ($P=0.966$) times were higher than the group without reflux. However the odds of 3 positive for one way 0.292 ($P=0.367$) times was lower than control group. Considering the number of cases, we rely only on descriptive statistics for other groups.

According to our findings, 61.8% of the samples were positive with regard to the level of serum PCT. One-half of those samples (38 people) who was diagnosed to be healthy using VCUG had a normal level of serum PCT. However, 30 people (88.2%) of the samples diagnosed to be healthy

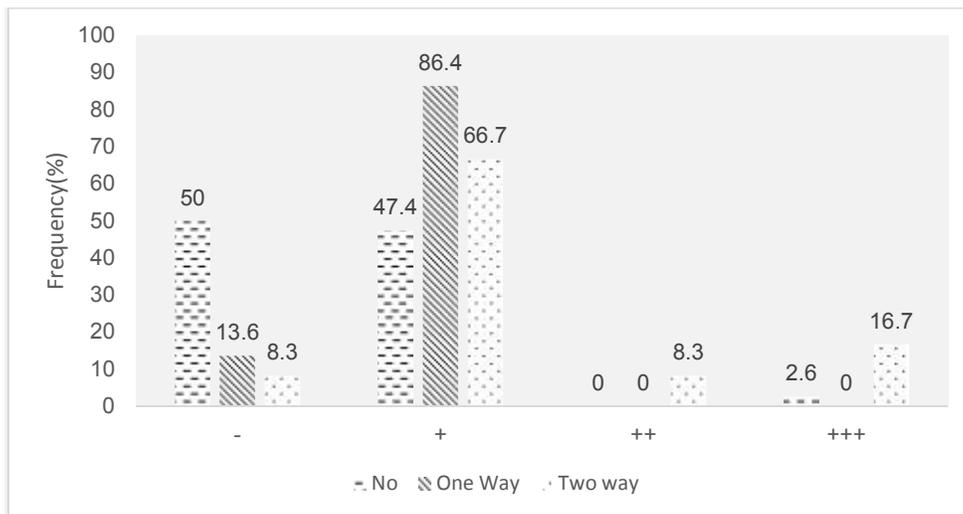


Fig. 1. The frequency of the diagnosis of VUR based on the evaluation method

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

Group	VCUG	Procalcitonin		Kappa	Odds ratio	P-value
		Control number (%)	Case number (%)			
Total	Control	38 (50)	38 (50)	0.3	7.5	<0.0001
	Case	4 (11.8)	30 (88.2)			
Boy	Control	13 (68.4)	6 (31.6)	0.51	27	0.003
	Case	0 (0)	6 (100)			
Girl	Control	19 (38)	31 (62)	0.196	3.67	0.028
	Case	4 (14.3)	24 (85.7)			

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 44% and 90%, respectively. In this respect, 50% of the samples diagnosed by serum level of PCT were false positive and 11.8% were false negative. It meant that sensitivity and specificity of PCT measurement were 88.2% and 50%, respectively. Globally, the odds of negative VUR were 7.5 times higher than positive VUR. In addition, the odds of negative VUR were 27 times and 3.67 times higher than positive VUR in males and females, respectively.

The kappa score for the level of serum PCT was 0.3 ($P < 0.0001$) (Table 2).

Accordingly, the sensitivity of the level of serum PCT for the female samples was 85% and for male samples were 100%. Additionally, the specificity of the serum PCT for the female and male samples was 38% and 68.4%, respectively. The positive predictive value of serum PCT for the female and male samples was 43% and 50% respectively (Table 3).

5. 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 [13-22].

PCT has been demonstrated to be correlated to both acute pyelonephritis and late renal scars and predict VUR in children with UTI [15].

In our study, 78 children (75.7%) were female. The median age of the samples was 21 months with an interquartile range between 10 and 36 months. Although, 69.1% of them had no vesicoureteral reflux, 20% and 10.9% 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% of children respectively [17].

The serum level of PCT more than 0.5 ng / ml is considered abnormal and may indicate sepsis [13]. 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 [12, 13].

According to our findings, 61.8% of the samples were positive with regard to the level of serum PCT. One-half of those samples (38 people) who was diagnosed to be healthy using voiding cystourethrogram had a normal level of serum PCT. However, 30 patients (88.2%) 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 [20]. This study revealed no significant differences in PCT values in children with and in those without VUR and VUR grade [20]. In other study, a meaningful relationship between VUR grade more than 3 and the clinical decision regulation was not found [17]. In children with VUR grade ≥ 3 , PCT is remarkably higher than in children with no or low-grade VUR (15). The association of PCT with VUR in children with febrile UTI remains controversial. The positive and negative predictive values of the level of serum PCT were 44% and 90%, respectively. In this respect, 50% of the samples diagnosed by using level of serum PCT were false positive and 11.8% were false negative. 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 [19]. The positive predictive value of the level of serum PCT for the female and male samples was 43% and for the male ones was 50%. Nowadays, 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 of serum level of PCT in the diagnosis of pediatric UTI and VUR.

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

Symmetric measures						
Gender			Value	Asymp. std. error ^a	Approx. T ^b	Approx. sig.
Girl	Measure of Agreement	Kappa	.196	.083	2.203	.028
	N of Valid Cases		78			
Boy	Measure of Agreement	Kappa	.510	.152	2.924	.003
	N of Valid Cases		25			
Total	Measure of Agreement	Kappa	.278	.073	3.464	.001
	N of Valid Cases		103			

a. Not assuming the null hypothesis;b. Using the asymptotic standard error assuming the null hypothesis

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	III	
Female	VCUG	Healthy	Count	19 _a	31 _b	50
			% within VCUG	38.0%	62.0%	100.0%
			% within Procalcitonin	82.6%	56.4%	64.1%
	III	Count	4 _a	24 _b	28	
		% within VCUG	14.3%	85.7%	100.0%	
		% within Procalcitonin	17.4%	43.6%	35.9%	
	Total	Count	23	55	78	
		% within VCUG	29.5%	70.5%	100.0%	
		% within Procalcitonin	100.0%	100.0%	100.0%	
Male	VCUG	Healthy	Count	13 _a	6 _b	19
			% within VCUG	68.4%	31.6%	100.0%
			% within Procalcitonin	100.0%	50.0%	76.0%
	III	Count	0 _a	6 _b	6	
		% within VCUG	0.0%	100.0%	100.0%	
		% within Procalcitonin	0.0%	50.0%	24.0%	
	Total	Count	13	12	25	
		% within VCUG	52.0%	48.0%	100.0%	
		% within Procalcitonin	100.0%	100.0%	100.0%	
Total	VCUG	Healthy	Count	32 _a	37 _b	69
			% within VCUG	46.4%	53.6%	100.0%
			% within Procalcitonin	88.9%	55.2%	67.0%
	III	Count	4 _a	30 _b	34	
		% within VCUG	11.8%	88.2%	100.0%	
		% within Procalcitonin	11.1%	44.8%	33.0%	
	Total	Count	36	67	103	
		% within VCUG	35.0%	65.0%	100.0%	
		% within Procalcitonin	100.0%	100.0%	100.0%	

Each subscript letter denotes a subset of procalcitonin categories whose column proportions do not differ significantly from each other at the .05 level

6. 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.

CONSENT

As per international standard or university standard, patients' guardians' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

The measurement of serum PCT as a non-invasive method was carried out with the consideration of all ethical principles such as obtaining the patient's permission, and waiving the measurement costs for the patients. It was incorporated into the routine blood sampling taken from the patients. The patients' guardians were informed of the study method, the voluntary nature of participants and the possibility of withdrawal from the study at any time without being penalized.

ACKNOWLEDGEMENTS

This study was supported financially (grant number: 93414) by Qom University of Medical Sciences, Qom, Iran. The authors would like to thank all participants in this research project whom without their collaboration the development of this article would be impossible.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Elder JS, Vesicoureteral Reflux. In: Elder J, Behrman RE, Kliegman RM, Jenson HB. Nelson textbook of Pediatrics. 17th Ed. Philadelphia: W.B Saunders company. 2016;2562-4.
2. Akhavan Sepahi M, Sharifiain M, Sadr Moharrerpour S. Pediatric Vesicoureteral Reflux Approach and Management. Caspian J Pediatr March. 2017;3(1):209-14.
3. Sharifian M, Mohkam S, Akhavan Sepahi M. Spontaneous resolution of vesicoureteral reflux (VUR) in Iranian children: a single center experience in 533 cases. Nephro-Urol Mon. 2011;3:191-5.
4. Fukui S, Watanabe M, Yoshino K. Intrarenal reflux in primary vesicoureteral reflux. International Journal of Urology. 2013;20(6):631-6.
5. Akhavan Sepahi M, Eftekhari SS, Rashidinia Sh, et al. The Relationship between Urinary Reflux and Nephrolithiasis in Children: A Cross-Sectional Study. Int J Pediatr. 2017;5(5):4965-73. DOI: 10.22038/ijp.2017.22728.1898
6. Akhavan sepahi M, Eftekhari SS, Shahmoradi S, Talebizadeh M, Rashidinia Sh, Hejazi SS. Metabolic and Anatomic Abnormalities Associated with Pediatric Nephrolithiasis: a Cross-Sectional Study. Int J Pediatr. 2017;5(5):4833-38. DOI: 10.22038/ijp.2017.22705.1896
7. Tej K. Mattoo, Ranjiv Mathews, and Indra R. Gupta, Vesicoureteral Reflux and Renal Scarring in Children in: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Golstein S. Pediatric nephrology. 7th Ed. Baltimore: Williams Wilkins. 2016;P1715-1748.
8. Sorkhi H, Hashemi M. Renal scan in children with vesicoureteral reflux and urinary tract infection. Journal of Mazandaran University of Medical Sciences. 2005;15(47):78-83.
9. Carrol ED1, Thomson AP, Hart CA. Procalcitonin as a marker of sepsis. International Journal of Antimicrobial Agents. 2002;20(1):1-9.
10. Muddassir Muhammad Shaikh MM, Hermans LE, Jacob M. van Laar. Is serum procalcitonin measurement a useful addition to a rheumatologist's repertoire? A review of its diagnostic role in systemic inflammatory diseases and joint infections. Rheumatology. 2015;54(2):231-240.
11. Song JU, Lim SY, Kwag HJ, Lim SY, et al. The Clinical Utility of Serum procalcitonin In Immunocompetent Patients with Pleural Tuberculosis. Acta Medica Mediterranea. 2016;32:447.
12. Hassan Ghobadi, Shahrzad M. Lari, Firouz Amani, Shahram Habibzadeh, Amirhosein Karimi, Farhad Pourfarzi. The Impact of Treatment on Serum Level of Procalcitonin in Patients with Active Pulmonary

- Tuberculosis. Journal of Cardiothoracic Medicine. 2014;2(4):238-242.
13. Janota J, Simák J, Stranák Z. Procalcitonin--a marker of systemic infection and multiorgan dysfunction: characteristics of the gene and protein. Cesk Fysiol. 2001;50(3):119-24.
 14. Leroy S, Adamsbaum C, Marc E, et al. Procalcitonin as a predictor of vesicoureteral reflux in children with a first febrile urinary tract infection. Pediatrics. 2005;115:706-709.
 15. Sandrine Leroy, Alain Gervais . Procalcitonin: A Key Marker in Children with Urinary Tract Infection .Advances in Urology; 2011. Article ID 397618, 7 page227.
 16. Sun HL1, Wu KH, Chen SM, Chao YH, Ku MS, Hung TW, Liao PF, Lue KH, Sheu JN. Role of procalcitonin in predicting dilating vesicoureteral reflux in young children hospitalized with a first febrile urinary tract infection. Pediatr Infect Dis J. 2013;32(9):e348-54.
 17. Leroy S, Bouissou F, Fernandez-Lopez A, Gurgoze MK, Karavanaki K et al. Prediction of High-Grade Vesicoureteral Reflux after Pediatric Urinary Tract Infection: External Validation Study of Procalcitonin-Based Decision Rule. PLoS ONE. 2011;6(12):e29556. DOI:10.1371/journal.pone.0029556
 18. Rahimzadeh N, Otukesh H, Hoseini R, Shadani S, Hooman N. Serum procalcitonin level for prediction of high-grade vesicoureteral reflux in urinary tract infection. Iran J Kidney Dis. 2014;8(2):105-8.
 19. Gendrel D1, Leroy S, Bréart G, Chalumeau M. Procalcitonin and prediction of vesicoureteral reflux in pediatric urinary tract infection. Bull Acad Natl Med. 2007;191(8):1731-43.
 20. Ji-Nan Sheu, Hung-Ming Chang, Shan-Ming Chen. The Role of Procalcitonin for acute pyelonephritis and subsequent renal scarring in infants and young children, Pediatric Urology. 2011;2002-2007.
 21. Mohkam M, Farshid Kompani , Alireza Ghafari .Diagnostic Values of Serum Procalcitonin in Kidney Diseases. Journal of pediatrics nephrology. 2015;3(1):7-12.
 22. Leroy S, Romanello C, Galetto-Lacour A, et al. Procalcitonin is a predictor for high-grade vesicoureteral reflux in children: Meta-analysis of individual patient data, The journal of Pediatrics. 2011;159(4):644-651.

© 2020 Sepahi et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/61185>*