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Comparing serum levels of interleukin-6 (IL-6) in acute pyelonephritis versus acute cystitis in 6 months to 12 years old children

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Abstract

Background and Objectives: Urinary Tract Infections (UTI) is a common disorder in pediatrics and early diagnosis is important. However, in young children diagnosis is problematic. A problem is variety in sign and symptoms and for exact diagnosis in some case we need expensive modalities. Thus, new way is needed. IL-6 at last decades was preferred to UTI diagnosis and upper/lower involvement differentiation. According to contrariety in IL-6 accuracy this study was performed to learn about diagnostic accuracy of plasma IL-6 in UTI diagnosis and its power for differentiating upper from lower involvement.

Methods: At this descriptive study, 83 patients were included and examined for Interleukin 6 value in both urinary tract diagnosis and upper/lower involvement differentiation. Demographic characteristic like age, gender, history, physical examination beside of blood tests like white blood cell count, ESR, CRP, IL-6 were done and results listed. Descriptive parameters were reported by mean and frequency and for statistical analysis was performed using t-test in SPSS v.16. ROC curve was checked for diagnosed value.

Results: In this study 83 patients (14 control group, 33(39.8%) cystitis, 36(43.4%) pyelonephritis) with 3.93±3.069 mean age enrolled. Age distribution at this study was 20, 63 for males and females, respectively. The IL-6 level in cystitis was higher than control and but was not significant. In ROC curve sensitivity and specify of IL-6 for cystitis were 52%, 50% and for pyelonephritis 60%, 50%, respectively.

Conclusion: According to this study, IL-6 is not a good biomarker for Urinary tract infection and differentiation upper tract involvement from the lower tract. A wide range of Il-6 level and useless of this biomarker can be due to gender distribution, time of disease presence, bacterial virulence and other factors. Therefore, studies on large sample is recommended.

Keywords: Cystitis, Interleukin 6, Pyelonephritis

Background

Urinary tract infection is a pediatric common disease. 20% of total medical consults and 5.3% referred neonatal to the emergency has urinary tract Infection (UTI)(1). UTI prevalence in male is 1% and in females 1-3 %. Disease sign and symptoms varied in different age group. Therefore, the diagnosis of UTI in the neonate and young children need more evaluation (2).

Today primary paraclinical evaluation of UTI diagnosis is based on white blood cell count, ESR, CRP, urine analysis and urine culture. Differentiating upper UTI from lower UTI using Dimercaptosuccinic Acid scan is an expensive way and expose the child to radiation (3).

IL-6 is a new biomarker suggested for UTI diagnosis. Interleukins at first was known as leukocytic drive chemokine. Today, 35 subtype of in-

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terleukins are found to have a remarkable role in immunity response. IL-6 is a multifunction cytokine that has a role in differentiation and B cell maturation immunoglobulin and acute phase protein production, bone marrow stimulation, mesangial cell growth and macrophage monocyte phagocytic complex activation (4). In last decades' studies, IL-6 urine and blood level measurement were seemed to be helpful for UTI diagnosis and in someone useful differentiate Upper involvement from lower (5). According to contrariety in IL-6 accuracy this study was performed for diagnostic accuracy of plasma IL-6 in UTI diagnosis and its power for differentiating upper from lower involvement.

Methods

At this descriptive study, 83 patients were included and examined for interleukin 6 value in both urinary tract diagnosis and upper/lower involvement differentiation. Urinary infection complains such as fever, nausea, vomiting, costovertebral tenderness plus urination complains in pyelonephritis and criteria like dysuria and frequency without a systematic sign and symptoms of cystitis were inclusion criteria. In case of group patient, with negative urine excluded. In both groups, a chronic disease especially those IL-6 involved in them (e.g. rheumatoid arthritis, cancers, asthma, and infectious disease and psychogenic disease) and taking immunosuppress drugs were excluding criteria. Control group patient selected from non-urinary tract diagnosis or complains. All patient's parents signed Informed consent. Demographic characteristic like Age, gender history, and physical Examination done and listed.

Urine analysis, Urine culture and a blood sample collected from cases. Urine analysis was done by Kimia Pazhohan urine dipstick made in Iran and microscopic analysis. Cell count was done by K.X_21 made in Japan. ESR was done by Hast Aran Teb Erythrocyte sedimentation rate reader made in Iran. CRP done by ENISON made in Iran. In Sanandaj's Be'sat hospital library. For interleukin 6 evaluation first get 5cc whole blood then kept 30 min in 25°C. After that centrifuged at 3500 rpm for15 min. plasma collect and frozen in -70°C. After completing sample collection IL-6 measured by Bioscience Elisa kit made in China and read by Awareness Elisa reader made in United State. Among all of these tests, urine culture is considered as a definitive diagnostic test. Descriptive parameters report by Mean and frequency and for Statistical Analysis done t-test in SPSS v.16. ROC curve drowns for diagnosed value.

Table 1. Fever and chilling distribution in UTI Groups

	Fever (%)	Chilling (%)
Positive	47(68.1%)	17(31.9%)
Negative	22(24.6%)	52(75.4%)

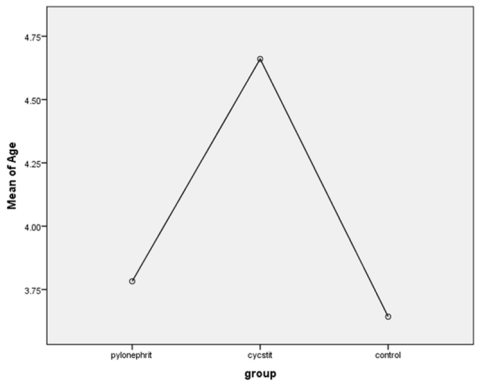


Fig. 1. Age distribution in study groups

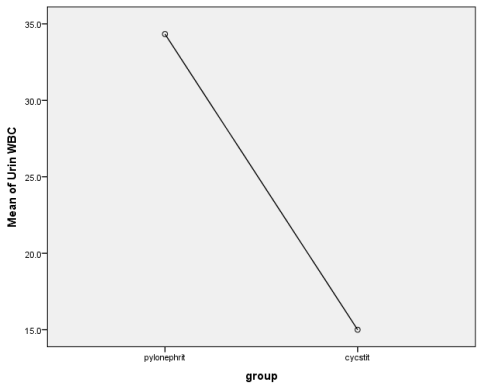


Fig. 2. Urine WBC count mean in study groups

Results

In this study, 83 patients evaluated. Demographic characteristics showed mead age 3.93±3.069 (minimum 6 months, maximum 12 years old), 63(75.9%) female and 20 (24.1%) male. Mean age of cystitis group was higher (Figure 1). 33(39.8%) were cystitic (6 male, 23 female), 36(43.4%) pyelonephritic and 14(16.9%) were control patients. CRP level distribution showed 32.5% negative, 6% 1+, 8.4% 2+, 10.8% 3+ and 14.5% 4+. In UTI group analysis is shown in Table 1.

Blood and urine WBC count mean in pyelonephritis was higher than cystitis group (Figures 2, 3). The higher bacterial *Spp.* was *E.coli* (Table 2).

Interleukin-6 in plasma level in cystitis showed a little higher level than another group. Tree patients' blood sample excludes for mascaras (Table 3).

IL-6 distribution by age showed that under 4y/o and up to 11 y/o has higher blood level (Figure 4).

Except for *Klebsiella,* in other bacterial species

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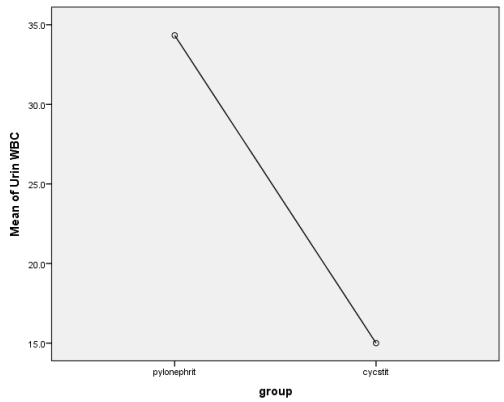


Fig. 3. Blood WBC count mean in study groups

Table 2. Bacterial Species cultured in UTI Groups

Species	Frequency (%)
E.coli	48(57.8)
Klebsiella	8(9.6)
Enterobacter	7(8.4)
Staph	3(3.6)
Acinetobacter	1(1.2)
Contaminated	1(1.2)
Proteus vulgaris	1(1.2)
Negative (Control)	14(16.9)

IL- 6 Level higher than the control group. Highest IL-6 level seen in uncommon species (Table 4).

IL-6 level except in negative lower urinary tract sign and symptoms has a higher level than control. In a patient with presenting sign and symptom has a higher level than negative ones (Table 5).

ROC curve sensitivity and specify of IL-6 for cystitis 52%, 50% and for pyelonephritis 60%, 50% respectively. Cut point for IL-6 in pyelonephritis is 123.100 and for cystitis is 122.700. Diagnostic accuracy in pyelonephritis 0.547 and for cystitis is 0.510 (Figures 5 AND 6).

Discussion

Urinary tract infection has remarkable incidence in pediatric but unspecific symptom and signs make early diagnosis and starting treatment difficult. Thus, finding a new way for early diagnosis is important. Previous methods such as use ESR, CRP with white cell count, urine analysis and disease Natural course has not enough sensitivity – specify for diagnosis in infant to young child. New biomarkers use in last decades trying to solve this problem. IL-6 is a new biomarker for UTI diagnosis. Some studies dedicate that urinary and plasma level of IL-6 can help for distinct upper UTI from lower and determine the severity of disease (1-5).

In this study 83 patients (14 control group, 33(39.8%) cystitis, 36(43.4%) pyelonephritis) with 3.93±3.069 mean age were studied. Age dis-

Table 3. IL-6 distribution in study groups.

	Mean	Std. Deviation	Std. Error	95% CI for Mean	95% CI for Mean	min	Max
				Lower Bound	Upper Bound		
pyelonephritis	193.317	134.2601	22.3767	147.890	238.744	47.1	483.2
cystitis	203.567	151.5177	27.6632	146.989	260.144	54.6	546.0
control	167.714	112.1863	29.9830	102.940	232.489	37.0	462.0
Total	192.680	136.5295	15.2645	162.297	223.063	37.0	546.0

Table 4. IL-6 distribution by bacterial species

Species	Mean	N	Std. Deviation
Proteus vulgaris	417.600	1	.
Acinetobacter	419.000	1	.
Staph	297.400	3	163.6092
Enterobacter	233.071	7	161.3307
E.coli	171.773	48	130.0441
Klebsiella	163.225	8	181.9039
Contaminated	155.200	1	.
Control	167.714	14	112.1863
Total	185.716	83	138.8074

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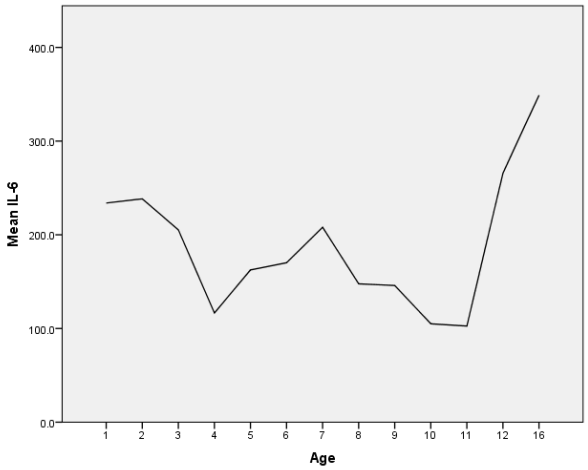


Figure 4. IL-6 distribution by age

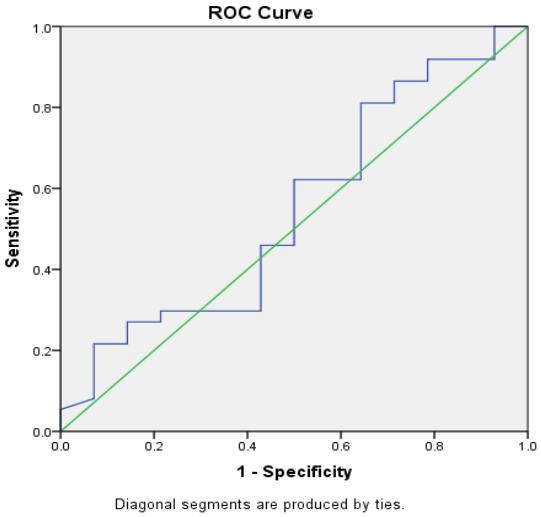


Fig. 5. ROC Curve for IL-6 diagnostic value of pyelonephritis

tribution was 20 and 63 for males and females respectively. Interleukin 6 level in cystitis was higher than control and cystitis but this was not significant. In ROC curve sensitivity and specificity of IL-6 for cystitis were 52%, 50% and for pyelonephritis 60%, 50% respectively.

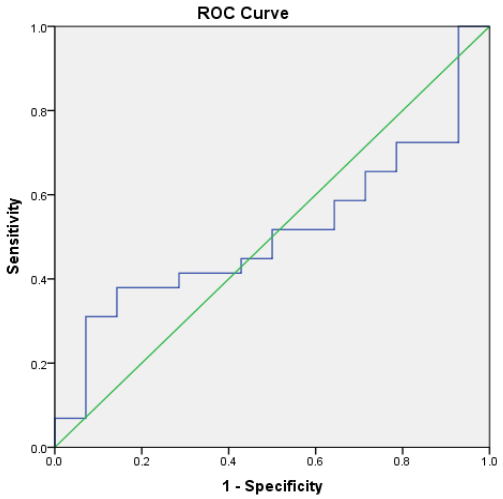


Fig. 6. ROC curve for il-6 diagnostic value of cystitis

E.coli was the most frequent germ in this study similar to Galanakis et al (6), Jantausch et al (7) Spasojević et al (8), Mahya et al (9), Krzemień et al (10), Benson et al (11), Nickavar et al (12) studies. In this study Klebsiella in the second rank. Uncommon germs more frequent in cystitis group but pyelonephritis common germs are frequent.

The IL-6 level in cystitis was higher than other groups. Control group has less IL-6 mean but statistically was not significant. Barbara et al (13), Sharifi et al (15), Krzemień et al(17), Galanakis et al(12), Tullusl et al (13) studies just showed a significant difference in pyelonephritis against control. SHEU et al (14), Azab et al (13), Rodríguez et al (15), Sheu et al (16) studies showed the significant higher level of IL-6 in UTI patients but pyelonephritis was more than cystitis. Mahyar et al (16), Morozov et al (17), Benson et al, Otto et al showed higher level of IL-

Table 5. IL-6 distribution by sign and symptoms presentation

Upper Urinary tract sign and symptoms	Mean	N	Std. Deviation
Negative	187.826	53	143.8219
Positive	194.475	16	149.3794
Lower Urinary tract sign and symptoms	Mean	N	Std. Deviation
Negative	27.300	2	38.6080
Positive	194.206	67	143.2984
Fever	Mean	N	Std. Deviation
Negative	182.141	22	162.2866
Positive	192.751	47	136.4217
Chilling	Mean	N	Std. Deviation
Negative	191.990	52	147.3314
Positive	181.347	17	137.4724
Control	167.714	14	112.1863
Total	185.716	83	138.8074

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6 in UTI patient but statistically not significant.

In this study, patients under 3 years and up to 11 had a higher level of Il-6. In some studies IL-6 raised by age. In this study, case finding difficulty was a problem for gender adjustment. Thus, according to some studies, this contrary result against other studies may be due to gender effect. Galanakis et al study found no relation between gender and IL-6, though Benson et al (11) found a higher level of Il-6in females in UTI.

Conclusion

According to this study, IL-6 is not a good biomarker for urinary tract infection and differentiation of upper tract involvement from the lower tract. Financial and technical issues like positive urine culture case finding make study hard to do in a larger sample. A wide range of Il-6 level may be affected by the patient difference. Ecological factors and race can make difference in gene expression and single nucleotide polymorphism. Bacterial virulence is another factor in inflammation degree which mentioned in some other studies. Response delay in immunity system can change cytokine level. In future studies start time of symptom and signs had to be considered for certain evaluation of cytokine during disease. Thus, one reason of IL-6 wide range may be inflammation start time.

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Conflicts of interest: None declared.

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