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Assessment the Effect of Dexamethasone on Urinary Cytokines and Renal Scar in Children with Acute Pyelonephritis

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Introduction. One of the most serious complications of acute febrile pyelonephritis in children is the development of renal scar. This study aimed to investigate the effect of dexamethasone on urinary cytokine levels and renal scar in children with acute pyelonephritis.
Methods. In a double-blind randomized clinical trial, 60 children aged 3 months to 12 years with acute febrile pyelonephritis enrolled. The experimental group was treated with a combination of antibiotic and dexamethasone, and the control group underwent treatment with antibiotic and placebo. The urinary levels of interleukin -6 (UIL-6) and -8 (UIL-8) were measured before treatment as baseline and were repeated four days later.
Results. 52 cases (23 patients with mean age of 34.19 ± 30.82 months in the dexamethasone group, and 29 patients with mean age of 50.55 ± 44.41 months in the control group) completed the study. In the control group, the UIL-6 and UIL-8 level became significantly lower after four days treatment ($P < .05$). In the dexamethasone group, there was a statistically significant difference between both UIL-6 and UIL-8 levels before and after treatment ($P < .05$). In patients who had scar on DMSA scan, the mean UIL-8 and UIL-6 levels were significantly high before and after treatment.
Conclusion. Results of this study showed that dexamethasone plus antibiotic have no clear superiority to antibiotic therapy alone in decreasing inflammatory cytokines and scar formation. We found out that patients with scar had sustained high levels of biomarkers before and after treatment.

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common infections in childhood, which can be associated with a serious risk of long-term complications such as renal scar, hypertension and even renal failure.[1] UTI is found in about 5% of febrile infants under one year old and 2% of febrile children between 1 to 5 years.[2,3] Renal scar due to UTI depends on age at the onset of disease, the lower the age, the greater the likelihood of complications, and the incidence of renal scar after acute pyelonephritis is between 5% and 57%.[4-6] Children with kidney scar are at risk of ESRD, hypertension and pregnancy complications in the future.[6] Therefore proper diagnosis and management of UTI is a significant aspect of preventive measures.[4] The standard treatment of febrile UTI is the intravenous use of antibiotics such as cephalosporins or aminoglycosides.[7,8] One of the measurement factors in the diagnosis and

treatment of urinary inflammation is modification of cytokines such as interleukins (IL), which can be helpful to recognize the response to therapy.[9-13]

IL-1, -6, and -8 are components of mucosal and systemic responses, which are released following gram-negative bacterial infections, and due to lipopolysaccharide and the invasion by the organism itself.[14-16] IL-6 is one of the inflammatory mediators with known function in the early stages of immune response to every bacterial infection. It has some regenerative activities and is involved in fever development and C-reactive protein (CRP) growth. IL-8 is a cytokine that causes migration of inflammatory cells to the site of inflammation.[14] It was suggested that the urinary and serum levels of these two cytokines are increased in children with UTI.[14,17] However, IL-6 and -8 are reported to be found with high concentrations in the urine of children and adults with UTI comparing with healthy ones.[18,19] However there are several controversial information with regards to the level of urinary IL-6 (UIL-6) and -8 in acute pyelonephritis.[20,21] Following the successful use of steroids in the treatment of acute bacterial meningitis to reduce its long-term complications, the hypothesis of simultaneous use of steroids along with appropriate antibiotics in other infectious diseases seems to be somewhat acceptable.[22] Steroids can be used in this regard for their anti-inflammatory effects.[13] Thus, the use of anti-inflammatory or antioxidant drugs along with antibiotics may have an appropriate anti-inflammatory effect and reduce the subsequent complications of urinary tract infections.[23-27] The aim of this study was to evaluate the effect of dexamethasone on urinary cytokine levels and renal scar in children with acute pyelonephritis who referred to the tertiary center; Bouali-Sina hospital in Sari, Iran.

MATERIALS AND METHODS

This double-blind clinical trial was conducted on 60 children aged 3 months to 12 years with acute pyelonephritis who referred to Bouali-Sina hospital in Sari, Iran. This project had been registered in Iranian Registry of Clinical Trials (IRCT20110531006660N4).

Inclusion Criteria

Inclusion criteria consisted of febrile children diagnosed with acute pyelonephritis. These children referred with chief complaint of fever with or without urinary tract symptoms, and in urine analysis, some elements of urinary tract infections such as white blood cells, leukocyte esterase, nitrite, and bacteria were active and had positive urine culture obtained from midstream clean-catch specimen, catheterized specimen or by suprapubic bladder aspiration. Positive urine culture in midstream clean-catch specimen was defined as more than 50,000 colony forming units (CFU)/mL in symptomatic patients or more than 10^5 colonies in asymptomatic patients. In the catheter technique 10^3 and in suprapubic technique, any colony count was considered positive.

Exclusion Criteria

Patients with a previous history of urinary tract infection, urinary tract abnormalities, renal failure, renal scarring and taking antibiotics were excluded.

Study Design and Methods

This study was approved by the ethics committee of research and technology deputy of Mazandaran university of medical sciences, and written informed consent were obtained from parents of all enrolled patients. Subsequently, the patients were randomly divided into two equal experimental and control groups of 30 patients that were matched in terms of age and sex. The experimental group (dexamethasone group) was treated with combination of antibiotic (ceftriaxone 80 mg/kg/d) and dexamethasone 0.15 mg/kg every 6 hours for 4 days intravenously, and the second group (control group) underwent treatment with antibiotic (ceftriaxone 80 mg/kg/d) and placebo (normal saline). The antibiotic was changed based on a sensitivity test in resistant cases. At the beginning of the study, the clinical laboratory tests including CBC diff, ESR, CRP, Blood culture, UIL-6, UIL-8, and ultrasonography associated with DMSA were performed for all participants. After four days, CBC diff, ESR, CRP, UIL-6, UIL-8 were repeated along with urinary culture. DMSA was repeated for patients with an abnormal scan after four to six months. VCUG following negative culture was performed for patients who had an abnormal ultrasound, abnormal scan or atypical urinary tract infections. Urine specimens were taken from all of the patients to measure interleukins 6 and 8 by spectrophotometry at a wavelength

of 450 nm for 4 days before and after treatment. Clinical symptoms of the patients were recorded at the beginning and during the treatment. Patients who had not completed the trial were excluded from the study. During this study, 7 patients in the dexamethasone group and one patient in the control group had left the study, and 52 patients completed the trial.

Statistical Data Analysis

Collected data were analyzed using SPSS 21 software by an appropriate statistical procedure such as descriptive analytic statistics including central tendency and distribution, depends on the variables obtained from the research questionnaire. To compare qualitative data, chi-square test and, if necessary, Fisher's exact test was performed and t-test was used to compare quantitative data. $P < .05$ was considered statistically significant.

RESULTS

Of total 60 patients, 52 cases completed the trial. The patients put in two groups; group1 those who treated with dexamethasone and antibiotic (23 patients, 91.3% female) and group 2 that treated with antibiotic and placebo (29 patients, 93.1% female). The mean age between the two groups was not different (34.19 ± 30.82 mo vs. 50.55 ± 44.41 mo, $P > .05$). Table 1 shows the demographic data and clinical findings of the patients on admission. As shown in Table 1, there was no statistically significant difference in age, sex and clinical findings between the two groups ($P > .05$).

Table 1 shows the initial results of laboratory tests of patients in both groups. As shown in Table 1, BUN was significantly higher in the dexamethasone group than the control group ($P < .05$), but the value lies in the normal range in both groups. In contrast, the WBC count and PMN in the control group ($P < 0.05$), was significantly higher than the dexamethasone group ($P < 0.05$). However, the results of other examinations including the blood level of creatinine, ESR, CRP, urine analysis, urinary WBC count, urinary red blood cell count, bacteria count in urine, positive urine culture, UIL-6, UIL-8, Abnormal Ultrasonography, and Positive Scan of DMSA were not significantly different between the two groups (Table 1). Blood cultures were negative in all of the patients.

After 4 days of treatment, only one patient in the dexamethasone group had a positive urine culture ($P > .05$). Although, the white blood cell count was not significantly different between the two groups, the percentage of lymphocytes and PMNs were

Table 1. The Results of Initial Laboratory and Imaging Assessment of the Patients in Dexamethasone and Control Group Before and Four Days After Treatment

Tests	Time of Therapy					
	Before Therapy			After Therapy		
	Dexamethasone Group	Control Group	*P*	Dexamethasone Group	Control Group	*P*
CBC						
WBC ($\times 10^3$)	11.20 ± 0.6	16.03 ± 0.6	< .05	9.3 ± 4.5	8.7 ± 3.2	> .05
Lymph, %	41 ± 19	31 ± 16	> .05	54.14 ± 14.01	54.14 ± 14.01	< .05
PMN, %	54 ± 19	64 ± 17	< .05	40.24 ± 16.04	40.24 ± 16.04	< .05
ESR	42.47 ± 33.16	53.75 ± 37.40	> .05	24.17 ± 20.06	41.58 ± 31.72	< .05
CRP, mg/dL	9.86 ± 14.02	17.68 ± 18.61	> .05	2.34 ± 4.90	6.93 ± 8.02	< .05
Positive Urine Culture	23 (100)	29 (100)	> .05	1 (4.3%)	0 (0%)	> .05
UIL-6, pg/mL	25.61 ± 10.20	20.33 ± 9.26	> .05	2.57 ± 3.99	3.19 ± 5.15	> .05
UIL-8, pg/mL	290.29 ± 437.70	497.56 ± 975.84	> .05	27.70 ± 61.71	102.76 ± 274.25	> .05
BUN, mg/dL	23.5 ± 5.70	20.06 ± 6.45	< .05	The test was not repeated in the acute phase of the disease.		
Cr, mg/dL	0.54 ± 0.07	0.56 ± 0.12	> .05	The test was not repeated in the acute phase of the disease		
Abnormal Sonography	4 (17%)	6 (21%)	> .05	The test was not repeated in acute phase of disease		
Scar on DMSA	2 (33)	4 (33)	> .05	The test was not repeated in the acute phase of the disease		
VUR	2 (20)	6 (46)	> .05	The test was not repeated in the acute phase of the disease		

BUN: Blood Urea Nitrogen, WBC: White Blood Cell, PMN: Polymorphonuclear, ESR: Erythrocyte Sedimentation Rate, CRP: C - reactive protein, RBC: Red Blood Cell, U/A: Urine Analysis, UIL-6: Urine Interleukin 6, UIL-8: Urine Interleukin 8, DMSA: Dimercaptosuccinic Acid

significantly higher in the control group ($P < .05$) than the dexamethasone group ($P < .05$). Moreover, the quantitative measurement of ESR and CRP showed that the rate of these two inflammatory markers in the dexamethasone group ($P < .05$) was significantly lower in comparison with the control group ($P < .05$) (Table 1). However, there was no statistically significant difference between the UIL-6 and UIL-8 levels in the two groups ($P > .05$) (Table 1). We compared the urinary levels of IL-6 and IL-8 in two groups before and four days after treatment in Table 2. In the control group, the UIL-6 and UIL-8 levels were reduced significantly with treatment (Table 2).

Table 3 presents the assessment of patients with normal and abnormal imaging studies.

The mean ESR in patients with an initial abnormal DMSA scan (68.41 ± 40.44) was significantly higher than the patients with normal primary DMSA scan (39.22 ± 29.24; $P < .05$). In addition, at the beginning of the study, the mean urine UIL-8 was significantly higher in patients with abnormal DMSA scan than in patients with normal scan (789.47 ± 1173.27 versus 219.57 ± 409.03; $P < .05$). However, the mean UIL-6 was not significantly different between patients with normal and abnormal scans (18.62 ± 47.49 pg/ml, 31.0 ± 51.76 pg/ml ; $P > .05$). The second DMSA performed 4-6 months later. Permanent kidney damage (scar) was found in 4 patients of the control and in 2 patients of the dexamethasone group ($P > .05$). The mean UIL-6 level before treatment in patients with and without abnormal scar was 24.06 ± 31.87 and 22.49 ± 51.12, respectively; which was not statistically significant ($P > .05$). Also, the mean UIL-8 level before treatment in patients with and without renal scar was 966.95 ± 1404.28 and 332.71 ± 657.18, respectively; that was not statistically significant ($P > .05$). In addition, UIL-6 measurement after treatment showed that the mean level of UIL-6 in patients with and without renal scar was 5.10 ± 8.09 and 2.63 ± 4.05, respectively; which was not statistically significant ($P > .05$). However, the mean UIL-8 level was 271.23 ± 578.89 in patients with a renal scar and 43.26 ± 83.10 in patients without a renal scar ($P < .05$). In fact, the mean UIL-8 level after treatment was significantly higher in patients who had a scar after 4 months. On the other hand; the comparison between urinary cytokine levels before and after treatment revealed that both IL-6 and IL-8 levels were reduced significantly four days after treatment in patients without scar but the levels did not change in patients with abnormal DMSA scan with any treatment (Table 3, Figure).

Table 3. The Urinary Levels of IL-6 and IL-8 in Patients with Normal and Abnormal Imaging Studies Before and Four Days After Treatment

ILs*	Before Therapy	After Therapy	*P*
DMSA			
Normal			
UIL-6	22.49 ± 51.12	2.63 ± 4.05	< .001
UIL-8	332.71 ± 657.18	43.26 ± 83.10	< .001
Scar			
UIL-6	24.06 ± 31.87	5.10 ± 8.09	> .05
UIL-8	966.95 ± 1404.28	271.23 ± 578.89	> .05
VCUG			
Normal			
UIL-6	30.36 ± 60.55	1.27 ± 1.27	< .05
UIL-8	229.44 ± 334.92	201.09 ± 505.90	< .05
VUR			
UIL-6	30.77 ± 50.38	4.63 ± 7.13	< .05
UIL-8	961.00 ± 1431.62	45.64 ± 84.50	< .05

ILs: interleukins presented as pg/mL.

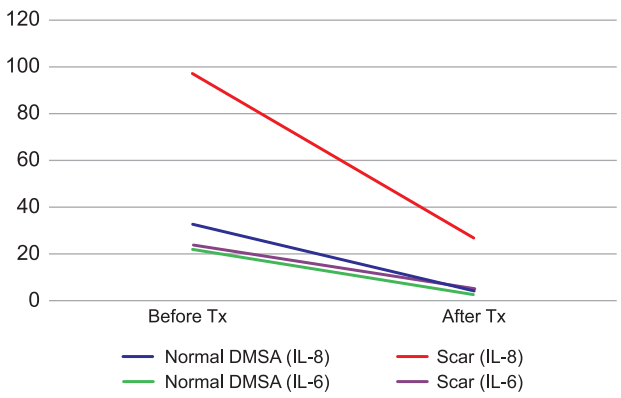

Figure. It shows the urinary levels of IL-6 and IL-8 in patients' normal and abnormal late DMSA scan before and four days after treatment. The IL-6 levels are presented as (pg/mL) and IL-8 levels as (pg/100 microliter)

Table 2. The Urinary Levels of IL-6 and IL-8 in Patients of Dexamethasone and Control Groups Before and Four Days After Treatment

	Dexamethasone Group			Control Group		
	Before Therapy	After Therapy	*P*	Before therapy	After therapy	*P*
UIL-6 pg/mL	25.61 ± 48.94	2.57 ± 3.99	< .001	20.3 ± 49.9	3.2 ± 5.2	< .001
UIL-8 pg/mL	290.29 ± 437.70	27.70 ± 61.71	< .001	497.56 ± 975.84	102.76 ± 274.24	< .05

Following the negative culture, VCUG was performed in 10 patients in the dexamethasone group and 13 patients in the control group. VCUG was reported abnormal in 2 patients in the dexamethasone group and 6 in the control group. However there was no significant difference between the two groups ($P > .05$). Comparing the patients with normal and abnormal VCUG, the mean UIL-6 level at the beginning of the study (30.36 ± 60.55 versus 30.77 ± 50.38, $P > .05$), and 4 days after the beginning of the study (1.27 ± 1.27 vs. 4.63 ± 7.13, $P > .05$) was not significantly different. The mean level of UIL-8 at baseline, in patients with normal and abnormal VCUG was 229.44 ± 334.92 and 961 ± 1431.62, respectively; which was significantly different ($P < .05$). Furthermore, 4 days after the beginning of the study, patients with abnormal VCUG had a mean UIL-8 level of 201.09 ± 505.90, while patients with normal VCUG had a mean UIL-8 level of 45.64 ± 84.50 of those with reflux, which was also significantly different between the two groups ($P < .05$).

Again; the comparison of urinary cytokines levels before and after treatment revealed that both IL-6 and IL-8 levels have been reduced significantly four days after therapy in patients with normal or abnormal VCUG results (Table 3).

DISCUSSION

UTI is an important pediatric infection both for morbidity and long-term complications.[3] We assessed the efficacy of dexamethasone on reducing the urinary IL-6 and IL-8 levels. We showed that there was no statistically significant difference between UIL-6 and UIL-8 levels before and after treatment. As expected, the antibiotic therapy leads to a critical decline in cytokine levels. The UIL was not reduced significantly in those with kidney scar. Dexamethasone administration had no significant effect on urinary levels or course of the disease.

The urinary and blood levels of IL-6 and IL-8 in patients with febrile UTI was assessed previously. It was suggested that urinary and serum levels of many cytokines are higher in pyelonephritic patients than healthy ones. Nickavar showed that urinary levels of IL-4, IL-6, and IL-8 levels are higher in patients with febrile UTI and decreased following antibiotic treatment.[9] Krzemień and co-workers studied on 35 children in three groups of febrile UTI, afebrile UTI, and asymptomatic bacteriuria. They found that the urinary levels of IL-6 and IL-8 were significantly higher in febrile patients than two other groups.[14] A similar finding has been reported by Tullus et al.[16] and by Mohkam et al.[15] They mentioned in their studies that the levels of inflammatory cytokines were significantly higher in patients with acute pyelonephritis than healthy children. The probable effect of corticosteroids on UTI was suggested by Haraoka in an animal study two decades ago. He showed that high dose prednisolone prevents kidney scar formation in female rats with Serratia infection.[27] POHL in another animal study assessed the effect of corticosteroids in piglets with induced UTI and VUR. They concluded that in cases with severe pyelonephritis administration of prednisolone lead to 3 times more chance of resolution (27% vs. 9%).[28] Recently, Sharifian et al. studied the levels of UIL-6 and UIL-8 in 34 children with acute pyelonephritis, who were treated with ceftriaxone and steroids and 20 patients with the same diagnosis, treated with ceftriaxone alone. In their study, the combination of dexamethasone and antibiotic versus antibiotic alone significantly decreased the urinary concentration of interleukins ($P < .05$). They concluded that the administration of steroid significantly reduces the levels of UIL-6 and UIL-8 in patients with acute pyelonephritis, and suggested that corticosteroids may be effective to prevent renal scars following febrile UTI. They did not find a correlation between mentioned cytokines and the results of DMSA and VCUG tests.[29] In our study, the urinary levels of interleukins were decreased with antibiotic treatment with or without corticosteroid. Our finding is not surprising, we expect to reduce inflammatory mediators with proper antibacterial therapy. We found higher levels of cytokines in patients with later scar both in the acute phase and after proper treatment. This means that in some patients the inflammatory process will remain active. The sustained process may progress to later scar formation and permanent kidney damage. Similarly, the abnormality of cystography had no effect on cytokine levels and response to therapy. The finding is true based on the developmental knowledge of VUR that is an anatomical defect. The inflammatory items of VUR are related to superimposed infection. Huang in a study performed on 84

patients (19 under combination therapy with oral methylprednisolone and antibiotics, and 65 only treated with antibiotics) showed that the incidence of the scar was approximately half as likely in group 1 patients than patients who received antibiotics alone (33% vs. 60%, $P < .05$). Based on their findings, they suggested that adjuvant therapy with oral prednisolone in children with acute pyelonephritis can reduce the incidence of renal scar.[26]

Nevertheless, similar to previous studies, our results showed that the antimicrobial treatment with or without dexamethasone significantly reduces the level of inflammatory markers of the acute phase (ESR and CRP) and decreases the level of inflammatory cytokines (UIL-6 and UIL-8). The unique finding of our study was the relationship between biomarkers and scar formation. In our study, the patients with late scar had high levels of interleukins in both initial assessments and after treatment. This means that with measuring urinary levels of IL-6 and IL-8, we can reveal the tendency for scar formation. This theory needs to be confirmed by further studies with larger sample size.

CONCLUSION

The results of this study showed that combination therapy with dexamethasone and antibiotic has no clear superiority to antibiotic therapy alone in decreasing inflammatory cytokines with no effect on reducing long-term change on renal DMSA scan. We found that patients with scar formation had sustained high levels of urinary biomarkers before and after treatment.

LIMITATIONS

One of the limitations of the present study was the low sample size. Due to insufficient financial resources, the minimum sample size was chosen. The low sample size influenced measurement and making comparison between factors considered for investigation in the studied subgroups.

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