Vitamin E as Adjuvant Treatment for Urinary Tract Infection in Girls with Acute Pyelonephritis

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Introduction. Vitamin E is a fat-soluble vitamin that functions as an antioxidant. The aim of this study was to investigate the effects of vitamins E supplementation in combination with antibiotics for the treatment of girls with acute pyelonephritis.

Materials and Methods. This double-blinded randomized controlled trial was conducted on 152 girls aged 5 to 12 years with a first acute pyelonephritis episode based on technetium Tc 99m dimercaptosuccinic acid (⁹⁹mTc-DMSA). They were randomized to receive a 14-day treatment with only antibiotics (control group; n = 76) and 14-day treatment with supplements of vitamin E (intervention group; n = 76) in addition to the antibiotics. Patients’ clinical symptoms were monitored for 14 days and urine culture was performed 3 to 4 days and 7 to 10 days after the start of the treatment and its completion, respectively. All of the girls once underwent DMSA scan 4 to 6 months after the treatment.

Results. During the follow-up days, the mean frequency of fever (P = .01), urinary frequency (P = .001), urgency (P = .003), dribbling (P = .001), and urinary incontinence (P = .006) were significantly lower in the intervention group compared to the control group. There was no significant difference in the results of urine culture 3 to 4 days after the start of treatment (P = .16) and 7 to 10 days after its termination (P = .37). There was also no significant difference between the results of DMSA scan 4 to 6 months after the start of treatment (P = .31).

Conclusions. Vitamin E supplementation has a significant effect in ameliorating sign and symptoms of UTI. However, further studies are recommended to confirm these findings.

INTRODUCTION

Urinary tract infections (UTIs) are common in childhood, affecting up to 3.5% of children in the United States annually.¹ Urinary tract infection is a serious bacterial infection because of its potential to produce renal scarring.² The 3 basic forms of UTI are pyelonephritis, cystitis, and asymptomatic bacteriuria.³ Clinical pyelonephritis is characterized by any or all of the following: abdominal, back, or flank pain; malaise; nausea and vomiting; and occasionally, diarrhea.⁴ Pyelonephritis is the most common serious bacterial infection in infants who have fever without an obvious focus.⁴ Overall, involvement of the renal parenchyma is termed acute pyelonephritis.⁴ Only up to two-thirds of children with a UTI accompanied by fever have acute parenchymal infection, with acute lesions on technetium Tc 99m dimercaptosuccinic acid
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In girls, 75% to 90% of all acute pyelonephritis episodes are caused by *Escherichia coli*, followed by *Klebsiella* and *Proteus*. It has been suggested that bacterial characteristics and the host defense play significant roles in the development of the scars in pyelonephritis. It has also been proposed that oxygen-free radicals play a role in renal scar formation after an acute pyelonephritis model in monkeys and mice. 

Recent experimental studies demonstrate that oxygen-free radical scavengers and antioxidants can reduce tissue damage and renal scarring during acute and chronic pyelonephritis. Antioxidant vitamins A, E, and C increase tissue protection from oxidative stress. Recently, it has been shown that both vitamins E and C decrease lipid peroxidation and augment the activity of antioxidant enzymes in the kidneys of diabetic rats. Vitamin E acts as a chain-breaking antioxidant and is an efficient pyroxyl radical scavenger, which protects low-density lipoproteins and polyunsaturated fats in membranes from oxidation. In addition to the cases mentioned regarding the role of oxidative stress in the pathophysiology of kidney diseases such as pyelonephritis and the effect of antioxidant vitamins on it, it has been reported that the pathology of the infectious process and host defenses against infection are apparently connected with a modulation of prostaglandin biosynthesis in the host. Infection, and especially the antigenic stimulus represented by the infection, may dramatically increase prostaglandin and cyclic nucleotide levels within minutes after a challenge. There is growing evidence that prostaglandin may regulate immune responses, and at elevated levels, prostaglandin may be immunosuppressive.

Vitamin E is an effective inhibitor of prostaglandin synthetize in certain tissues, and as an antioxidant it may prevent the oxidation of arachidonic acid in the biosynthetic pathway leading to prostaglandin. It is conceivable then that some of the biological functions of vitamin E may be connected with its modulation of prostaglandin synthesis. Several reports demonstrated that vitamin E is effective in protecting human from bacterial infection. This protection has been associated with increased antibody titer, and phagocytosis. Tengerdy and Brown demonstrated that production of prostaglandin in bursa homogenates of *E. coli*-infected chickens was reduced by supplementation of vitamin E. This was corroborated by Likoff and colleagues. On the basis of these observations, a hypothesis is proposed that the disease protective effect of vitamin E is connected with its antioxidant inhibitory effect on prostaglandin modulation caused by vitamin that may counteract prostaglandin modulation caused by the infectious process, thereby triggering host defense mechanisms. All these may lead to increased resistance to infection. Given the limited information regarding the supplementary effect of vitamin E in children with acute pyelonephritis, we decided to conduct a study in this area. Since UTI is more common in girls due to their shorter urethras, and boys suffering from UTI usually have underlying anatomical or functional abnormalities of the genitourinary tract that confound the study, we restricted our research to girls with pyelonephritis.

MATERIALS AND METHODS

**Participants**

This double-blind randomized controlled trial study was conducted from 22 April, 2012 to 21 November, 2013 on the patients admitted to the Department of Pediatrics of Amir Kabir Hospital and Vali Asr Hospital, in Arak, Iran. Participants included 5- to 12-year-old girls who had developed a form of acute pyelonephritis, for the first time and had indications of hospitalization due to UTI. With respect to the study conditions, these indications were defined as mild to moderate dehydration requiring rehydration and intravenous antibiotic therapy. Girls with repeated vomiting, severe UTI-induced dehydration, or bacteremia were not included in the study. The study was approved by the Ethics Committee of Arak University of Medical Sciences and a written consent was obtained from all patients’ parents or guardians. The patients could also withdraw liberally from the study at any time. The researchers were committed to the Declaration of Helsinki throughout the research.

The children and their parents were interviewed and underwent laboratory examinations in order to assess the inclusion criteria. These examinations included medical history of UTI symptoms (fever, frequency, urgency, dribbling, dysuria, urinary incontinence, and abdominal pain) urinalysis and

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urine culture, ultrasonography of the abdomen and pelvis, voiding cystourethrography, computed tomography, and ⁹⁹ᵐTc-DMSA scintigraphy. The midstream catch method was used for urine culture.² The genital area was washed from front to back with soap and water 3 times and intermediate urine samples were collected in sterile bags and transferred to the hospital laboratory. In order to perform the urine culture and confirm the result, urine samples with infected medium were excluded from the study and urine samples prepared using the sterile method underwent analysis and culture for the second time.² Contamination of the culture medium was defined as a positive urine culture without pyuria.

If the urine culture showed more than 10,000 colonies of a single pathogen and the child was symptomatic (including fever, urinary frequency, urgency, dribbling, dysuria, urinary incontinence, and abdominal pain), the child was considered to have UTI.³²,³³ Since *E coli* is the most common cause of UTI and for easier cloning of the subjects for UTI factor organism, only the patients with UTI resulted by *E coli* were included in the study. Since this study aimed at analyzing urine samples with *E coli* sensitive to ceftriaxone and cefixime, *E coli* isolated from urine cultures underwent sensitivity test for evaluating their resistance or sensitivity to ceftriaxone and cefixime antibiotics. The evaluation was performed using the disk diffusion method. For this purpose, *E coli* was isolated from culture samples and underwent disk diffusion sensitivity test with the Kirby-Bauer method based on the CLSI M100-S22 (Clinical Laboratory Standards Institute M100-S20) protocol on 2010.³⁴ Antibiotic susceptibility disks were provided by Padtan Teb Company (Tehran, Iran).

**Renal Dimercaptosuccinic Acid Scintigraphy**

Since DMSA scintigraphy is the gold standard method for the diagnosis and localization of acute pediatric pyelonephritis,² all the girls qualified for the study's initial assessments underwent this scan for the evaluation of acute pyelonephritis. Girls with diagnosed renal scarring after DMSA scan were not included in the study. Renal scintigraphy was performed 3 to 4 hours after injection of a weight-scaled dose of DMSA. Acute scintigraphic pyelonephritis was defined as focal or diffuse areas of decreased DMSA uptake without evidence of cortical loss, and renal scar was defined as areas of negative DMSA uptake.²,³⁵

**Inclusion and Exclusion Criteria**

The children were included if they were female, aged 5 to 12 years old, had a medical history and symptoms of UTI and diagnosed with acute pyelonephritis based on fever (without any source other than UTI) and evidence of renal inflammation on DMSA scan, and had positive urinalysis and culture results only for *E coli* sensitive to ceftriaxone and cefixime. Informed consent from the parents was obtained for participating in the study and proper adherence to the study protocol after discharge from hospital was ensured. Patients with any of the following were excluded from the study: a diagnosis of renal scarring based on the results of DMSA scan; history of any form of UTI; vesicoureteral reflux, symptoms of renal abscess, renal and urinary tract calculus, urinary tract obstruction, emphysematous pyelonephritis, renal hypoplasia, ectopic kidney, and any unilateral or bilateral renal anomaly based on ultrasonography, CT scan, and voiding cystourethrography findings; neurogenic bladder; history of voiding dysfunctions; anatomical problems of the genitalia such as labial adhesion, due to trauma, surgery, and congenital anomalies; history of allergy to vitamin E or its intolerance; history of diabetes mellitus, immunodeficiency, and organ transplantation; administration of antibiotics or vitamin E at least 5 days before the start of the study; severe sepsis and bacteremia; and severe dehydration.

**Study Protocol**

Considering the prevalence of UTI, sample size was determined at 152 (α = 0.05, β = 0.2). After assessment of the girls and their parents, they were randomly assigned into the intervention or control groups each with 76 participants. Medications were administered for 14 days in a way that all girls underwent routine UTI treatment. The treatment included 50 mg/kg/d to 75 mg/kg/d of intravenous ceftriaxone in 2 divided doses during hospitalization and 8 mg/kg/d of oral cefixime in 2 divided doses after discharge. Other than the routine treatment, the intervention group was administered 100 IU of oral vitamin E on a daily basis, 1 daily tablet, and the control group was administered placebo. Placebos were similar to vitamin E regarding their
shape, color, and size. Antibiotics were made by Jaber Ibn Hayyan (Tehran, Iran) and vitamin E and its placebo were made by Raazak (Tehran, Iran). Vitamin E and the placebo were administered in unnamed capped containers with a label containing the code of each medicine by a group other than the groups who examined and followed up the patients. The participants were unaware of the type of administered medicine.

The assessment of clinical response and the follow-up of patients were conducted by research assistant who was unaware of the type of medicine administered to patients for 14 days. As long as the girls were hospitalized, medications were administered by the rendering physician and staff. After the girls were discharged, the parents were provided with the necessary training for administering medicine to their children. They were also told to refer 7 to 10 days and 4 to 6 months after the treatment for repeated urine culture and DMSA scan, respectively.

All of the patient information was recorded in their clinical information forms. The forms included their demographic information, the results of urine culture 3 to 4 days after the start of the treatment and 7 to 10 days after its termination, the results of DMSA scan 4 to 6 months after the treatment, and the presence or absence of clinical symptoms (fever, frequency, urgency, dribbling, dysuria, urinary incontinence, and abdominal pain) during

Random allocation and interventions flowchart.
14 days of their follow-up.

Antibiotic susceptibility test was also carried out using the disk diffusion method along with urine culture to prove the possible existence of only 1 type of disease-causing organism and also measure the sensitivity of *E. coli* to administered antibiotics. It was aimed to exclude participants from the study in the case of recurrence of UTI with another bacterium, multiple bacteria, or *E. coli* resistant to antibiotic treatment.

Fever was defined as a body temperature increase (oral temperature) above 38.5°C without a source except for UTI; frequency was defined as increased frequency of urination twice as before; urinary incontinence was defined as urination outside the control of patient; dribbling was defined as involuntary urinary cessation and its restoration; dysuria was defined as feeling pain or burning when urinating; urgency was described as immediate need to urinate; and abdominal pain was defined as pain and discomfort in the abdominal cavity.4

The results of urine culture and DMSA were recorded in patients’ clinical information forms at specific times and 4 to 6 months after the treatment, respectively. All the renal scans were reviewed secondarily by 2 independent nuclear medicine experts who were unaware of the treatment that had been assigned to the patients.

Exclusion criteria during follow-up were as follows: (1) the absence of cooperation or satisfaction for continuing the participation; (2) the recurrence of UTI according to the results of urine culture during follow-up with more than 1 type of bacterium, an organism other than *E. coli* or with an *E. coli* resistant to administered antibiotics; (3) intolerance of oral vitamin E; (4) irregular use of medication; (5) comorbidity of febrile diseases other than UTI during the follow-up requiring the consumption of any other antibiotics, especially those used in this study; and (6) re-infection with any type of UTI between the second urine culture and repeated DMSA scan. When a child was excluded from the study for any reason, she was randomly replaced with another matching participant eligible according to the terms of the study and inclusion and exclusion criteria. The Figure illustrates the study recruitment process.

The collected data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 18.0, SPSS Inc, Chicago, Ill, USA),
and the chi-square test or the Fisher exact test and the Student \( t \) test were used for comparisons. \( P \) values less than .05 were considered significant.

RESULTS

In this 18-month study, 307 girls with UTIs were assessed against the inclusion and exclusion criteria. Sixty-eight of the girls were excluded and were replaced with other qualified participants. Overall, 93 girls with UTI were randomly analyzed based on the inclusion and exclusion criteria. Among 62 girls who were excluded during the follow-up, 38 (55.8%), 9 (13.2%), and 21 (30.8%) were excluded due to parental dissatisfaction for continuing participation, development of a febrile infection other than UTI requiring antibiotic treatment, and recurrence of UTI discordant with the conditions for continuing the participation, respectively.

The mean age of the participants was 5.8 ± 2.2 years old. This figure was 6.1 ± 2.5 years and 5.5 ± 2.0 years for the intervention and control groups, respectively (\( P = .14 \)). The frequencies of symptoms in the intervention and control group are presented in Tables 1 and 2. The average frequencies of fever, urinary frequency, urgency, dribbling, and urinary incontinence was significantly lower in the intervention group than the control group during the 14 days of follow-up, while no significant difference was observed in dysuria and abdominal pain between the groups.

There was no significant difference in the results of urine culture 3 to 4 days after the start of treatment and 7 to 10 days after its termination (Table 3). Analysis of the results of DMSA scan 4 to 6 months after the start of the treatment indicated that the inflammation of the renal parenchyma completely subsided in 76 (100%) and 75 (98.6%) of the girls in the intervention and control groups, respectively (Table 3).

DISCUSSION

According to our study, although there was no significant difference in the results of urine culture and DMSA scan of girls receiving vitamin E and antibiotic and those receiving only antibiotic, it was indicated that vitamin E could be significantly effective in the treatment of the majority of common clinical symptoms in girls with acute pyelonephritis, such as fever, frequency, urgency, dribbling, and urinary incontinence. Sobouti and colleagues\(^{36}\) conducted a study on 61 children with the age of

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<th>Table 3. Result of Urine Culture and Dimercaptosuccinic Acid Scintigraphy (DMSA) in the Control and Vitamin E Groups</th>
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<th>Table 2. Girls and With Abdominal Pain, Dysuria, and Incontinency During the 14-Day Follow-up in the Control and Vitamin E Groups</th>
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1 month to 10 years with acute pyelonephritis to investigate the effect of vitamins A and E on the improvement of renal scarring in Iran from 2004 to 2006. In this clinical trial, the children were randomized into 3 treatment groups of 10-day treatment with only antibiotics (control group; n = 25) and 10-day treatment with supplements of vitamin A (n = 17) or vitamin E (n = 18) in addition to antibiotics during the acute phase of infection. Based on this study, a worsening of lesions, based on the second DMSA scan, was observed in 42.5%, none, and 23.3% of the control, vitamin E, and vitamin A patients, respectively (likelihood ratio, 26.3; P < .001). In another study, Sadeghi and colleagues37 investigated the effect of vitamin E on mouse models with acute pyelonephritis by *E. coli* in 2008. The results indicated that inflammation and fibrosis scores in the group undergoing treatment with only intraperitoneal ceftriaxone was significantly higher than the group undergoing treatment with antibiotics and vitamin E.

In a study on mouse models infected with pyelonephritis by *E. coli*, Bennett and colleagues38 indicated that antibiotic treatment of pyelonephritic rats with vitamins A and E resulted in significantly less kidney inflammation, as compared with untreated rats or rats treated with antibiotic alone. According to our study, 14 days of supplementary administration of vitamin E along with antibiotic treatment had no significant effect on the reduction of renal inflammation during 4 to 6 months of follow-up compared to antibiotic treatment alone. The reason was that no evidence of renal inflammation was observed in the DMSA scan of almost all of the members of both groups 4 to 6 months after the start of the treatment. This finding is inconsistent with those of similar studies. The only previous clinical study on the effect of vitamin E on UTI was the one by Sobouti and colleagues,36 which investigated its effect on the improvement of renal scarring (one of our study’s exclusion criteria). Therefore, it was different from our study.

CONCLUSIONS

Generally, based on the results of our study, although the administration of vitamin E supplement caused no significant difference with the administration of antibiotics alone in the results of patient’s short-term urine culture and 4 to 6 month follow-up of DMSA scan, its administration is recommended from the start of the treatment to decrease clinical symptoms in infected girls because of its significant effect on the improvement of clinical symptoms in the acute phase of UTI. However, future study is recommended in this area due to the lack of clinical evidence regarding the effect of vitamin E supplement on the treatment of UTI patients’ clinical symptoms, renal inflammation, and scarring and more importantly, recurrent UTI cases.

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CONFLICT OF INTEREST

None declared.

REFERENCES


