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Does hydrochlorothiazide prevent recurrent urinary tract infection in children with idiopathic hypercalciuria?

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Abstract *Objective:* Idiopathic hypercalciuria (IHC) has been recognized as a common disorder in childhood, and is a major factor in the formation of renal stones and urinary tract infections (UTIs). Since hydrochlorothiazide ameliorates hypercalciuria, we assessed its efficacy in preventing recurrent UTIs in hypercalciuric girls.
Materials and methods: This research was a single blind randomized clinical trial. One hundred 1—12-year-old girls, who were followed in pediatric nephrology outpatient clinics of two referral hospitals in Markazi Province of Iran, were recruited. All patients had IHC and at least two UTIs in 1 year, without any underlying anatomic or functional abnormality of urinary tract. Patients were randomly divided into two equal groups. One group received instructions regarding general preventive measures for UTI and the other group, in addition to these measures, received 1 mg/kg/day hydrochlorothiazide as morning dose. Then recurrence of UTI in the two groups was evaluated.
Results: The mean age was 7.28 ± 1.9 years. In both groups, the incidence of UTI recurrence was 66%.
Conclusion: On the basis of these results, we reject the hypothesis that treating hypercalciuria is beneficial in preventing repeated UTIs. The association between UTIs and IHC needs to be more closely studied and attention to eliminating confounding factors is necessary.

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Introduction

Urinary tract infection (UTI) is the most common urogenital system disease and the second most common bacterial infectious disease. One to two percent of children and 5 percent of girls acquire it and 25% of them will have recurrences in the first year. After two episodes of UTI the risk of recurrence increases to 50%. The importance of recurrent UTI is a rise in the risk of renal scars, hypertension, proteinuria and decreased renal function [1—5,16].

A recent addition to the risk factors of recurrent UTI is idiopathic hypercalciuria (IHC), an autosomal dominant disorder which is observed in 3—9% of asymptomatic children and 20% of children visiting nephrology hospitals [1,2,6,7].

Patients with IHC have higher levels of urinary calcium excretion and normal serum calcium concentration with no proven underlying cause. It seems that accumulation of calcium oxalate microcrystals and epithelial damage to renal tubules might lead to an increased rate of infection in these patients [8]. The epithelial damage not only prepares a site for colonization of bacteria, but also leads to voiding dysfunction and renal stone formation. These three factors foster propagation of UTI in these patients [2,10,11].

In some studies, heightened water intake, limitation of calcium and protein intake, and potassium citrate consumption have been recommended in these patients to prevent recurrent UTIs. Unfortunately, dietary limitations, forcing water intake, and potassium citrate (due to its unappealing taste and gastrointestinal side effects) are not suitable or practical treatment modalities in children [1,2,4,7].

Thiazide diuretics are easy to use, cheap, widely available, have few side effects, and are acceptable drugs in the treatment of hypercalciuria. Thiazides increase reabsorption of calcium in distal renal tubules and improve hypercalciuria, which leads to decreased recurrence of renal stones and maybe UTI too [5,12,13]. In a previous study, hydrochlorothiazide was used to treat 59 children with IHC and repeated UTI. No UTI recurrence was reported in 95% of these children [7]. On the other hand, in another study in 2001 performed on 124 children, thiazide had no significant effect in decreasing UTI recurrence [8]. Also, clinical progression of patients in another study in 2005 (75 cases) was not different from that of normocalciuric children [6]. Mahmoodzadeh and colleagues studied the prevalence of IHC in cases of vesicoureteral reflux and UTI, and reported a 1.54-fold increase in IHC compared to controls, although this was not statistically significant [14].

Concerning these results, we decided to assess the effectiveness of this drug in preventing recurrent UTIs in children. Since 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 IHC.

Materials and methods

This was a single blind randomized clinical trial. One hundred 1—12-year-old girls with no underlying anatomical or functional abnormalities of the genitourinary tract, who were followed in pediatric nephrology outpatient clinics in Valiasr and Amirkabir Hospitals of Arak, Iran, with IHC and at least two repeated UTI in 1 year, were included in the study. Recruitment started on 1 March 2010 and follow-up ended in September 2010. The sample number was calculated with regard to recurrence of UTI and prevalence of hypercalciuria ($\alpha = 5\%$, $\beta = 80\%$).

IHC was defined as a urine calcium to creatinine ratio of more than 0.2 in random urine samples or urinary calcium of more than 4 mg/kg body weight in 24-h urine samples. More than 100,000 microbial colonies per milliliter of clean-catch midstream urine sample obtained by free voiding or 10,000 colonies plus UTI symptoms were defined as urinary infection. Due to the lack of accuracy of urine output measurement techniques in pediatric patients, we didn't consider their urine output in this study. After a thorough history and physical examination, all patients underwent blood and urinary chemistry tests, sonograms and voiding cystourethrograms (VCUG). Based on these findings, children who did not have any underlying problems such as neurogenic bladder, urinary tract and renal abnormality, voiding dysfunction, secondary non-idiopathic hypercalciuria, and anatomical problems, including labial adhesion, were recruited. After obtaining written consents, patients were divided into two equal groups using simple random sampling. One group received instructions regarding general preventive measures for UTI such as: free fluid intake, daily needed frequency of urination, complete voiding, reduction of dietary salt intake, washing genitalia from front to back, and wearing loose cotton underwear. The other group, in addition to these measures, received 1 mg/kg/day oral hydrochlorothiazide as a morning dose [1,17,18].

None of the patients received prophylactic antibiotics. Follow-up cultures were repeated 48 h and 7—10 days after the commencement of treatment, and were then repeated monthly for 3 months (as the first three months after treatment is the most common period for UTI recurrence). Recurrence was defined as positive urine culture and fever which was documented via renal DMSA scan. In the case of recurrence, the patients were treated according to their urine culture and pathogen sensitivity for 14 days. In the second group, urine calcium to creatinine ratios were measured 1 month later and if they did not become normocalciuric the dose of thiazide was increased to 2 mg/kg/day.

Non-compliant patients and dropouts who missed follow-up visits were excluded from the study and were replaced with matching compliant patients. Children who did not achieve the goal of urine calcium:creatinine < 0.2 with the 2 mg/kg/day dose of thiazide, assumed as being non-compliant, were also excluded. Fig. 1 illustrates the study recruitment process. Although the side effects of hydrochlorothiazide treatment, such as hypokalemia, hyponatremia and metabolic alkalosis, are rare considering the dosage used, we opted to record them during the study. We also warned the parents about signs and symptoms of dehydration and to cease administering the drug if vomiting or diarrhea occurred.

The recurrence of UTI in the two groups was evaluated and compared by Student *t*-test using SPSS software ver. 16. Before these steps, the research was explained to patients' parents and informed consents were obtained. The study protocol was approved by the Vice Chancellor for Research, Arak University of Medical Sciences, Iran.