

The Efficacy and Safety Of Using Hydrochlorothiazide As Adjuvant Therapy In Pediatric Urinary Tract Infections

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ABSTRACT

Background: Acute urinary tract infection is a common bacterial infection causing illness in infants and children. At age of seven, 8% of girls and 2% of boys will have at least one episode. Although drinking water and using home remedies are known to help to flush away bacteria and keeps them from sticking to the bladder wall, researches to test the efficacy and safety of hydrochlorothiazide's diuretic effect as adjuvant to the antibiotics in pediatric age groups are lacking, and so this research was to address this subject.

Objectives: To assess the effectiveness and the safety of hydrochlorothiazide as adjuvant therapy to the antibiotics in treating acute urinary tract infection in pediatric age group.

Type of the study: Case-control prospective study.

Methods: The study was done including eight hundred sixty five patients ((In_ & Out_ patients)): The patients included were aged from few hours (neonates) to 16 years old. Those who attended three pediatric hospitals- department of nephrology of: The Central Child Teaching Hospital, Al-Elwya Pediatric Hospital and Ibn Al-Baladi Hospital

Results: 215 patients in group 1 ((97.3%)) presented with cystitis and 6 patients ((2.7%)) with pyelonephritis, And In group 2, 243 ((96.4%)) with cystitis and 9 patients ((3.6%)) with pyelonephritis. The urine cultures were negative in ((76.4, 80.1, 85.9, 95.0 percentages of patients)) after ((10 days, 1 month, 3 months and 6 months respectively)) in group 1 vs. ((60.3, 68.60, 75.8, 85.3)) after the same periods

in group 2 ((p-value=0.04 at 10 days, 0.03 at 1 month, 0.04 at 3 month and 0.02 at 6 month)).

Conclusions: This research had concluded that 5 days of treatment with antibiotics and hydrochlorothiazide were effective and safe to treat children with urinary tract infection. Hydrochlorothiazide (as a diuretic and hypocalciuric agent) adjuvant to the antibiotics in pediatrics was safe and effective to: Decrease duration of treatment and hospitalization days, Improve clinical responses to antibiotics and Decrease risk of complications of UTI.

Keywords: hydrochlorothiazide, urinary, pediatrics.

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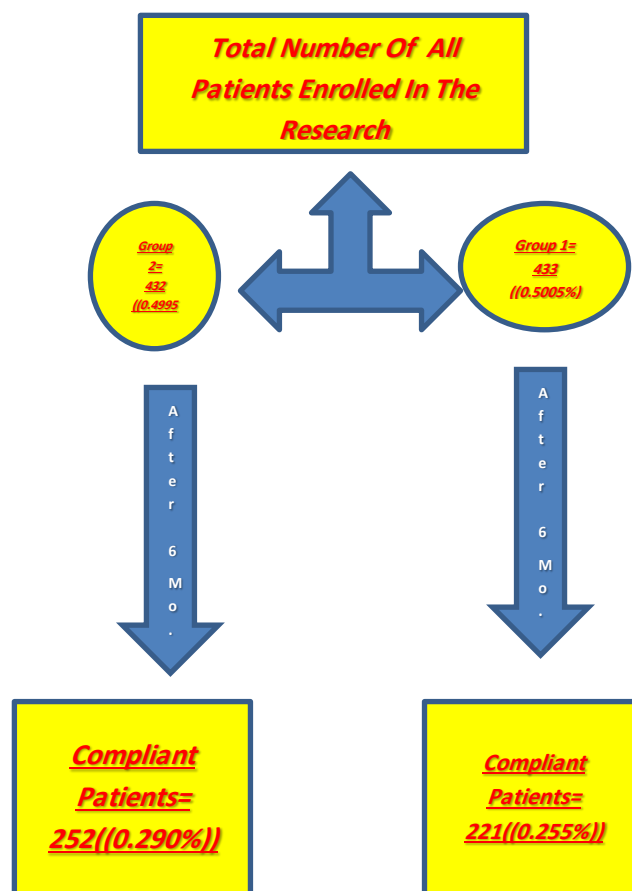
Acute urinary tract infection is a common bacterial infection causing illness in infants and children. At age of seven, 8% of girls and 2% of boys will have at least one episode. Although drinking water and using home remedies are known to help to flush away bacteria and keeps them from sticking to the bladder wall, researches to test the efficacy and safety of hydrochlorothiazide's diuretic effect as adjuvant to the antibiotics in pediatric age groups are lacking, and so this research was to address this subject. . Aims Of The Study was to assess the effectiveness and the safety of hydrochlorothiazide as adjuvant therapy to the antibiotics in treating acute urinary tract infection in pediatric age group.

Methods: A case control, prospective and multicenter study was done including eight hundred sixty five patients ((In_ & Out_ patients)): The patients included were aged from few hours (neonates) to 16 years old, Those who attended three pediatric hospitals- department of nephrology of: The Central Child Teaching Hospital, Al- Elwya Pediatric Hospital and Ibn

Al-Baladi Hospital Because of Uncomplicated acute urinary tract infection. The diagnosis of UTI depended upon collecting the patients' urine by The supra-pubic aspiration which was the method of choice for obtaining urine from: Uncircumcised boys with redundant or tight foreskin, From girls with tight labial adhesion, From children unable to void on request, and From neonates and infants. 2- A mid-stream urine collection for older children who have urinary control. 3- Sterile bag attached to the perineal area: and because of the high false positive rate in this method of urine collection, UTI was considered present only when a single uropathogen was identified on the urine culture and sensitivity done in this method of collecting urine. The diagnosis of UTI was considered when: The General Urine Exam (GUE) showed on light microscopy 5 pus cells or more per high power field. Urine culture: urine culture were done when urinalysis were negative in children with unexplained fever or with voiding symptoms. The other Laboratory studies were used beside the patients symptoms to differentiate between

pyelonephritis or cystitis: Complete blood count (CBC). Blood cultures (in patients with suspected bacteremia or sepsis). Renal function studies (i.e. serum creatinine and blood urea nitrogen). Electrolyte levels. Renal and bladder ultrasonography were performed in: Febrile UTI in infants aged 2-24 months. To differentiate between pyelonephritis and cystitis. Delayed or unsatisfactory response to treatment of a first febrile UTI. An abdominal mass or normal voiding (i.e. dribbling of urine). Recurrence of febrile UTI after a satisfactory response to treatment. Patients showing failure to thrive or gaining satisfactory weight during follow up. Voiding cystourethrography (VCUG) were performed: After a first febrile UTI only when renal and bladder ultrasonography revealed hydronephrosis, scarring, obstructive uropathy, or masses. After a second episode of febrile UTI. All the complicated UTI cases were excluded from the study e.g.: Presence of congenital urinary tract abnormalities. Presence of reflux nephropathy and /or crystals/ stones. Presence of GUT tumor. All the patients' parents were instructed to complete at least 5 days of antibiotic treatment and all patients were followed for 6 months as follow: Repeating the GUE after 5 days after treatment initiation. Repeating the GUE and urine culture 10 days after treatment initiation. Performing renal and bladder ultrasound beside a 3rd GUE and a culture testing after 1 month of ceasing treatment. Performing a 4th GUE and a culture testing 3 months after ceasing treatment. Performing a 5th GUE, a culture testing and a 2nd ultrasound 6 months after ceasing treatment. Eight hundred sixty five patients were divided to 2 groups: Group1: out of 433 patients included in our study, only 221 patients were compliant to the research conditions of completing treatment and had full follow up. 1. {Group1} (221 patients) were treated with: Hydrochlorothiazide tablets P.O. with 2 mg/kg/day, dose divided to 2 doses for the first 10 days for the initial course then decrease to 1 mg/kg/day once at night if the antibiotic treatment was needed to be prolonged. 2. The antibiotic treatment (Nalidixic Acid, Trimethoprime-Sulphamethoxizole, Nitrofurantoin, Cefotaxime or Amoxicilline-Clavulanate) started initially according to the patients' condition, age, known sensitivity to drugs and tolerance before the culture and sensitivity (C/S) results seen, then-after the antibiotic choice was changed according to the C/S results, the duration of the antibiotics was for 10 days if the patient showed full response or prolonged to 3-6 months if the response was unsatisfactory or the patient showed any complications. {Group2} (Control): out of 432 patients were included in this study, only 252 patients were compliant to the research conditions of completing treatment and had full follow up. Group2 (252 patients) received only the antibiotic treatment by the same dose for each drug, and for the same period as seen in group1. In the study, the patients were randomly divided in to two groups. {Group1} patients were treated with antibiotics and hydrochlorothiazide, {Group2} (The Control) patients were treated with antibiotics only. And in both, the patients were

followed for six months. Total number of patients who were fully compliant to the research conditions of completing treatment and full follow up were 473 patients (54.6% of the total 865 patients).



Parameters: Sex distribution: 174 patients enrolled in group 1 of the study were females ((78.7%)) and 188 in group 2 ((74.6%)). 2. Age: The mean ages of the patients were: 4.56±0.7 years in group1 and 7.2±0.4 years in group2. Presentation: 215 patients in group 1 ((97.3%)) presented with cystitis and 6 patients ((2.7%)) with pyelonephritis, And In group 2, 243 ((96.4%)) with cystitis and 9 patients ((3.6%)) with pyelonephritis.

Table-1-

	Total Number Of Patients	Sex Distribution: Female Number and %	Presentation	((Age Years
Group 1	221	174 ((78.7%))	215 ((97.3%)) With Cystitis & 6 ((2.7%)) with pyelonephritis	4.56±0.7
Group 2	252	188 ((74.6%))	243((96.4%)) With Cystitis & 9 ((3.6%)) With pyelonephritis	7.2±0.4

	% OF Patients Showing Clearance Of GUE Within 5 Days Rx	% OF Patients Needed 10 Days Rx To Clear GUE	% OF Patients With Symptomatic Improvement	Hospitalization Time ((Days))
GROUP 1	73.7%	7.7%	90.4%	5.6±0.4
GROUP 2	53.2%	12.7%	67.8%	8.2±0.8
THE p Value	<u>0.003</u>	<u>0.004</u>	<u>0.002</u>	<u>0.005</u>

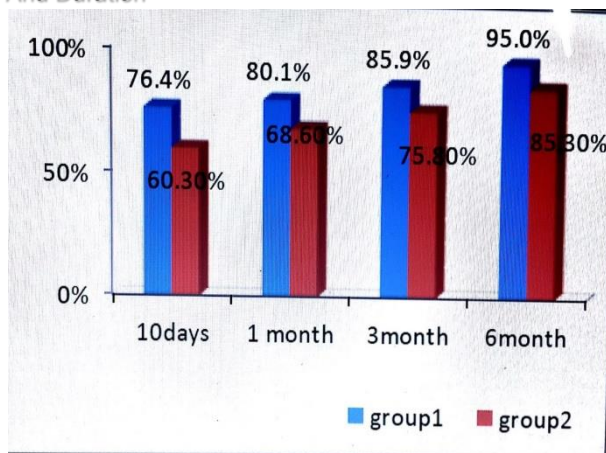
Table 2

The statistics of the research depended upon the regression analysis and the extraction of: The Mean. The p_ Value to determine statistical significance. Any p_ value more than 0.05 was considered statistically insignificant

Results: i. Clinical and laboratory response: 73.7% of the patients responded to treatment (monitored by clearance of general urine exam) within 5 days of treatment in group1 vs. 53.2% of patients in group 2 ((p-value=0.003)). 7.7% of patients in group 1 needed 10 days of treatment to clear the GUE vs 12.7% of the patients in group 2 ((p-value=0.004)). (90.4%) of patients in group 1 showed symptomatic improvement after 5

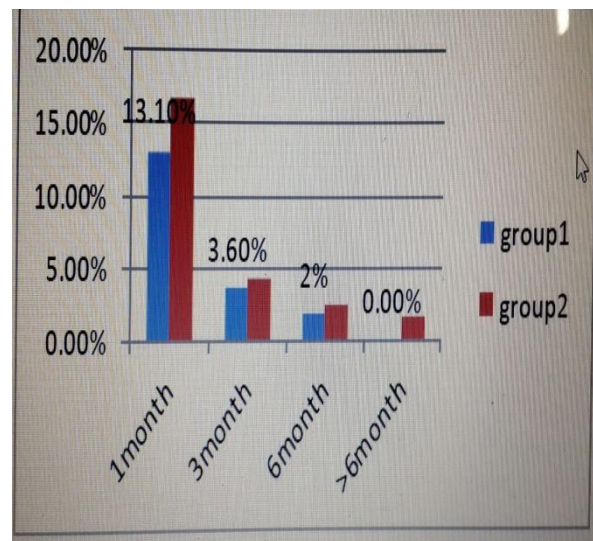
days of treatment initiation versus (67.8%) in group 2 ((p-value=0.002)). The urine cultures were negative in ((76.4, 80.1, 85.9, 95.0 percentages of patients)) after ((10 days, 1 month, 3 months and 6 months respectively)) in group1 vs. ((60.3, 68.60, 75.8, 85.3)) after the same periods in group 2 ((p-value=0.04 at 10 days, 0.03 at 1 month, 0.04 at 3 month and 0.02 at 6 month)).

Percentage Of Patients Become Negative Urine Culture And Duration



Hospitalization time: The mean days of hospitalization were 5.6±0.4 days in group1 and 8.2±0.8 in group2 ((p-value=0.005)). The need for a prolonged therapy: Twenty nine patients (13.1%) in group1 needed prolonged therapy for 1 month, and 8 patients (3.6%) for 3 months and 4 patients (1.8%) for 6 months and none of them needed a prolonged therapy for more than 6 months , while in group2, 42 patients (16.7%) needed prolonged therapy for 1 month, and 11 patients (4.4%) for 3 months and 6 patients (2.4%) for 6 months and 4 patients (1.6%) needed a prolonged therapy for more than 6 months ((p-value= 0.04, 0.1 and 0.05 respectively)).

Percentage Of Patients Needed A Prolonged Therapy



Complications During Treatment : Recurrence of infections: had been noted in 28 patients on group1, 16 of them are females while in group2, 44 patients had recurrence with 37 were females. Renal scarring: were noted in 3 patients in group2 and none in group1. There were no statistical differences regarding complications between group1 and 2 (p-value= 0.8, 0.9, 0.1 respectively). Hydrochlorothiazide side effects: Mild hypotension occurred in 4 patients, only one needed single shot of normal saline 20 cc per kg to correct the symptomatic hypotension and Muscle spasm occurs in 6 patients, No other side effects were noticed

Table -3-

	Recurrence Of Infection Number Of Patients And %	Renal Scarring Number Of Patients And %
Group 1	28 ((12.7%))	Zero ((0.00%))
Group 2	44 ((17.5))	3 ((1.2))
P_ Value	<u>0.002</u>	<u>0.03</u>

Discussion : Urinary tract infection affects females more than males as seen in table1 (p-value=0.001) in patients their mean ages were 4.56 ± 0.7 in group1 and 7.2 ± 0.4 in group2. In Lebanon, a study done by Rima H which included 675 cases with UTI with median age of 16 months, ((77.7%)) where females(7). UTI was more in males younger than 1 year (8). The prevalence of pyelonephritis in our study was ((3.2%)) as seen in table 3 by ultrasound. A Study done by Alijandro Hoberan showed that ((12%)) of children with UTI had pyelonephritis by ultrasound while the prevalence increased to ((61%)) by using renal scan. Ultrasound performed at the time of acute illness was of limited value (9). In table 4, ((62.7%)) of the patients with UTI responded to 5days of treatment while only ((10.4%)) needed 10days of treatment which was significant (p-value were 0.003 in group1 and 0.004 in group2) and ((26.9%)) of the patients needed treatment for more than 10 days. A study done by Michael M et al for 652 children with UTI showed that there was no significant difference in positive urine cultures between short duration (2 to 4 days) versus standard duration (seven to 14 days) of treatment (10). In our study, patients in group1 had better response to treatment by GUE (as seen in table 4 with p-value=0.02 at 5days of treatment), better clinical response (as seen in table5 with p-value=0.002 at 5days of treatment) and decrease the period of hospitalization (as seen in table 6) in comparison with group2. In group1, ((76.4%)) of the patients had negative urine culture while ((60.3%)) of the patients in group2 had negative urine culture after 10 days of treatment (p-value=0.03) as seen in figure1. In figure2, ((18.7%)) of the patients in group1 needed therapy for 1month and more while ((25.1%)) of the patients in group2 needed therapy for 1moth and more (p-value=0.04, 0.01 and 0.05 respectively). These significant responses seen in table4, 5, 6 and figure 1 and 2 can be explained by the use of hydrochlorothiazide (as a diuretic). Bacterial eradication from the urinary tract is partially dependent on urine flow and voiding frequency therefore, it seems logical to postulate a connection between urinary flow and the risk of urinary tract infections (UTIs) (11). However, experimental and clinical data on this subject are conflicting. Experimental studies concerning the effect of water intake and the use of diuretic drugs as adjuvant to the antibiotics on susceptibility and course of UTIs were predominantly performed in the sixties and seventies. Despite many open questions, there has been no continuous researches in this field especially in pediatric age group (11). The traditional herbal remedies e.g. Marshmallow Root, Juniper berries, Birch Leaves and Dandelion Tea used in the management of UTIs for their diuretic effects (12). Many authors recommend treatment of hypercalciuria, as it was seen in ((44%)) of the patients with recurrent UTI and ((10%)) of the patients with the first episode of UTI (13), by adequate fluid intake and salt restriction in the diet and if hypercalciuria persists in spite of these measures, hydrochlorothiazide may be required(14). Kaminska and Jung's study showed that treatment of hypercalciuria had reduced the episodes of UTI in ((43.6%)) of the patients (14). Moreover, Lopez et al observed that no further episodes of UTI occurred in ((95%)) of the children with recurrent UTI following the treatment of hypercalciuria (15). However, Yousefi et al, in a blind

and randomized clinical trial, rejected the hypothesis that treating hypercalciuria was beneficial in preventing repeated UTIs. They divided the patients who had recurrent UTI and idiopathic hypercalciuria into two groups. One group received general preventive instructions for UTI and the other group received hydrochlorothiazide in addition to preventive instructions. They found that the recurrence rate of UTI was ((66%)) in both groups (16). The beneficial effect of hypercalciuria treatment in reducing the episodes of UTI needs to be more accurately studied and attention should be paid to eliminating other contributing factors (17). In our study, ((15.2%)) of the patients had recurrent UTI, ((0.6%)) had renal scar and ((1.9%)) of the patients died during treatment (mainly neonates) because of progression of the disease to sepsis and 2 neonates died because of respiratory problems. Sheikh N. study found that approximately ((15%)) of children with UTI had renal scarring post infection and the likelihood of complications increases in children with upper UTI, recurrent UTI, vesicoureteral reflux or undiagnosed UTI. Early diagnosis and optimal management greatly reduces the likelihood of long-term complications (18). This high percentage of renal scar in Sheikh N. study may be explained by the use of more sophisticated techniques to diagnose renal scar other than renal ultrasound. Table8 shows side effects of hydrochlorothiazide, ((95.5%)) of the patients had no side effects with the mentioned dose (2mg/kg/day) and ((4.5%)) had only simple side effects and none of the patients need to stop treatment. In Iran, 100 girls treated by hydrochlorothiazide to treat abdominal pain due to hypercalciuria, no side effects were noticed among children during the study (for 6 months) and no one were excluded due to intolerance to hydrochlorothiazide, so the authors considered hydrochlorothiazide safe and inexpensive drug (19).

Conclusions : This research had concluded that 5 days of treatment with antibiotics and hydrochlorothiazide were effective and safe to treat children with urinary tract infection. Hydrochlorothiazide (as a diuretic and hypocalciuric agent) adjuvant to the antibiotics in pediatrics was safe and effective to: Decrease duration of treatment and hospitalization days, Improve clinical responses to antibiotics and Decrease risk of complications of UTI.

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