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Comparison of prevalence of hypercalciuria after intravenous injection of ceftriaxone versus ampicillin and cefotaxime in children with febrile infection

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Abstract

Background and aim: Ceftriaxone is a third generation Cephalosporin and is often used to treat infections of the upper gastrointestinal tract and urinary tract infections. Due to some reported side effects of these drugs, such as urinary stone formation which may be related to hypercalciuria, this study aimed to determine the effect of ceftriaxone in the treatment of urinary tract infection with urinary stone formation.

Methods: This cross-sectional study was carried out on 120 children from the age of 2 months to 14 years with febrile infections admitted to the Children's Hospital of Bandar Abbas in 2016. Patients were randomly allocated to two groups: The first group received a dose of ceftriaxone 100-50 mg/kg every 12 hours (depending on severity) and in the second group, ampicillin 50 mg/kg every 6 hours and cefotaxime 50 mg/kg every 8 hours were administered. For evaluation of hypercalciuria calcium to creatinine ratio (ca/cr) in random urine was used. Hypercalciuria was defined as Ca/Cr>0.6 in infants<1 years old and Ca/Cr>0.2 in infants>1 year old. Data was analyzed by IBM-SPSS version 21 through descriptive statistics, Chi-square, Fisher's exact test, independent samples t-test, and paired samples t-test. P-value less than 0.05 was considered significant.

Results: A total of 120 children were enrolled in the study (78 in the ceftriaxone group vs. 42 in the ampicillin and ceftriaxone group). Both groups were similar in terms of age, gender, creatinine ratio and pre-treatment Ca/Cr ratio, but the difference between the groups was compared after treatment (0.339±0.204 in the ceftriaxone group and 0.236±0.159 in ampicillin and cefotaxime group) (p=0.005). The prevalence of hypercalciuria in the group receiving ceftriaxone, 15 (19.2%) and in the group receiving Ampicillin 2 (4.8%) (p<0.03).

Conclusion: According to the information obtained from this study, we found out that ceftriaxone can increase the risk of hypercalciuria. Further studies with different populations could help to raise awareness of this issue.

Keywords: Ceftriaxone, Cefotaxime, Hypercalciuria

1. Introduction

1.1. Background and statement of problem

Fever is the most common cause of referral to health centers in children. Often, the etiology of fever is evident by physical examination and para-clinics. Bacterial infections are common etiology of fever, which can be treated with suitable antibiotics. Ceftriaxone is the treatment of choice for upper respiratory tract infections (pneumonia, otitis media) and urinary tract (pyelonephritis). Also, a combination of cefotaxime and ampicillin can be used with suitable coverage of gram positive and gram negative bacterial agents with synergistic effects (1). Ceftriaxone and ampicillin and cefotaxime, are common antibiotics used for febrile infections in children. Some studies have reported the increased risk of renal stone with ceftriaxone. The evidences in this regard are inadequate. Plasma half-

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life of ceftriaxone is 6 to 9 hours, and is higher in neonates. About 55% of its single dose excretes in urine and 45% excretes in the biliary tract which causes some complications in the biliary system (2-4). Common side effects are anemia, thrombocytopenia, hemolysis, nephrolithiasis, colitis, pseudocholelitiasis, and biliary sludge (5, 6). Recent evidence shows that ceftriaxone can cause hypercalciuria. Ampicillin is widely used for infections of urinary and respiratory infections and meningitis (7). Cefotaxime is a third generation cephalosporine which is used in respiratory, urinary, and skin infections and in peritonitis, and meningitis. Side effects such as hypercalciuria and biliary sludge are not reported in ampicillin use (7). Widespread use of ceftriaxone in febrile infections in children increases the risk of hypercalciuria and renal stones and gallbladder stones in these patients. Ampicillin and cefotaxime have similar anti-bacterial effects with no risk of hypercalciuria or renal stones. The exact mechanisms of ceftriaxone induced hypercalciuria is not clear. Also, limited evidence is available for prevalence of ceftriaxone induced hypercalciuria. More studies are needed to obtain enough evidence which can be applicable in management of patients with febrile infections.

1.2. Objectives

The general objective of this study was to compare the prevalence of hypercalciuria after intravenous injection of ceftriaxone versus ampicillin and cefotaxime in children with febrile infection in a pediatric hospital in Bandar Abbas in 2016.

2. Material and Methods

2.1. Study design and setting

This study was conducted on 120 children with fever and bacterial infection between 2 months and 14 years old referred to a pediatric hospital in Bandar Abbas in 2016.

2.2. Sampling

Considering the power of 80% and confidence interval of 95% and standard deviation of 0.16 for Ca/Cr ratio, a sample size of at least 93 patients were calculated to determine the difference of 0.1 in Ca/Cr ratio in two groups (8). Using convenience sampling, we selected 120 children from 2 months to 14 years old who were referred to a pediatric hospital in 2016, and were diagnosed to have bacterial febrile infection requiring ceftriaxone or ampicillin and cefotaxime. Convenience sampling helped us to reach the sample size with lower costs and to save time. Patients were randomly assigned into two groups either to receive 50-100 mg/kg ceftriaxone (based on disease severity) or ampicillin 50 mg/kg every 6 hours, and cefotaxime 50 mg/kg every 8 hours.

2.3. Outcomes

For assessment of hypercalciuria calcium to creatinine, ratio of random spot urine sample (mg) were used at 24 hours after antibiotic administration. Measures above 0.6 in neonates less than 1 years old and measures above 0.2 in children above 1 year were assumed to be hypercalciuria.

2.4. Data collection

For each patient, a checklist including demographic information (age, gender, place of residence, etc.), urine calcium to creatinine ratio before treatment and 48 hours after treatment were completed.

2.5. Ethical issues

A written informed consent was obtained from all the parents. Patients' information was kept confidential. The study is approved by the Ethics Committee of Hormozgan University of Medical Sciences (HUMS.REC.1394.140).

2.6. Statistical analysis

Data were analyzed by IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY, USA) using descriptive statistics Chi-square, Fisher's exact test, independent-samples t-test, and paired-samples t-test. P-value less than 0.05 was considered to be significant.

3. Results

3.1. Demographics

Among 120 children included in this study, 61 (50.8%) were male and 59 (49.2%) were female. Among 78 patients in the ceftriaxone group, 37 were male and 41 were female. Also, among 42 patients in the ampicillin and cefotaxime group, 24 were male and 18 were female. Baseline characteristics of the patients in both groups are compared in Table 1.

3.2. Main results of hypotheses

Mean Ca/Cr ratio was 0.339±0.204 in the ceftriaxone group and 0.236±0.159 in the ampicillin and cefotaxime group. The difference was statistically significant (p=0.005). Table 2 compares the prevalence of normal and abnormal Ca/Cr ratio in the two groups. There was no statistically significant difference between duration of hospitalization and Ca/Cr ratio in the two groups. As shown in Table 3, there was no significant difference in Ca/Cr ratio based on gender in the two groups (p>0.05); also, there was no significant difference in Ca/Cr ratio based on the age group (p>0.05).

Table 1. Baseline characteristics of patients in both groups

Variable	Classification	Ceftriaxone	Ampicillin and cefotaxime
Gender (percentage)	Male	37 (47.4 %)	24 (57.1 %)
	Female	41 (52.6 %)	18 (42.9 %)
Age (years)	>1	34 (43.6 %)	15 (35.7 %)
	<1	44 (56.4 %)	27 (64.3 %)
Duration of hospitalization (days)	2	24 (30.8 %)	13 (31 %)
	3	28 (35.9 %)	17 (40.5 %)
	4	26 (33.3 %)	12 (28.6 %)
Ca/Cr ratio		0.2 ± 0.091	0.195 ± 0.092

Table 2. Comparison of the prevalence of normal and abnormal Ca/Cr ratio in two groups

Group	Ca/Cr ratio		p-value (Chi-square test)
	Normal	Abnormal	0.03
Ceftriaxone	63 (80.8 %)	15 (19.2 %)	
Ampicillin and cefotaxime	40 (95.2 %)	2 (4.8 %)	

Table 3. Comparison of duration of hospitalization, gender, and age group based on Ca/Cr ratio

Variable	Group	Subgroups	Ca/Cr ratio		p-value (Chi-square)
			Normal	Abnormal	
Duration of hospitalization	Ceftriaxone (days)	2	20 (31.7 %)	4 (26.7 %)	0.910
		3	22 (34.9 %)	6 (40 %)	
		4	21 (33.3 %)	5 (33.3 %)	
	Ampicillin and cefotaxime (days)	2	13 (32.5 %)	0 (0 %)	0.596
		3	16 (40 %)	1 (50 %)	
		4	11 (27.5 %)	1 (50 %)	
Gender	Ceftriaxone	Male	27 (42.9 %)	37 (47.4 %)	0.097
		Female	36 (57.1 %)	5 (33.3 %)	
	Ampicillin and cefotaxime	Male	22 (55 %)	2 (100 %)	0.209
		Female	18 (45 %)	0 (0 %)	
Age	Ceftriaxone (years)	>1	24 (38.1 %)	10 (66.7 %)	0.067
		<1	39 (61.9 %)	5 (33.3 %)	
	Ampicillin and cefotaxime (years)	>1	13 (32.5 %)	2 (100 %)	0.089
		<1	27 (67.5 %)	0 (0 %)	

4. Discussion

This study was done on 120 children with febrile infection who were admitted to Bandar Abbas pediatric hospital for comparison of hypercalciuria after intravenous injection of ceftriaxone or ampicillin and cefotaxime. We found that the Ca/Cr ratio is significantly higher in the ceftriaxone group in comparison to the ampicillin and cefotaxime group.

4.1. Comparison of study results with similar studies

Takahisa Kimata et al. (8) have reported in their study in 2012 that urine Ca/Cr ratio is significantly higher in patients using ceftriaxone in comparison to amoxicillin. The serum calcium level was similar in the two groups before and after the intervention. There was no significant relationship between gender or age and hypercalciuria in the two groups. Similar findings were reported in our study. In contrast to our findings, there was a significant

relationship between duration of hospitalization and hypercalciuria in this study. The difference between the results of the two studies may be due to difference in sample size and race difference between the two groups. In contrast to our results Anoush Azarfar et al. found no significant difference in urine calcium to creatinine ratio in children receiving or not receiving ceftriaxone (9). The serum calcium level was not significantly different in the two groups before and after the study. This finding is similar to our findings. In this study, the researchers used placebo for the control group. We used ampicillin and cefotaxime in the control group. Both studies were carried out on Iranian children but the sample size was different in the two studies. Alper Otunctemur et al. have shown in their study that patients receiving ceftriaxone and cephalothin have higher levels of urine Ca/Cr ratio regardless of having kidney stones or not. Our results confirm these findings. In this study, the urine calcium level was similar in all groups before intervention. After treatment, the urine calcium level increased in both patients with and without kidney stones. These findings are similar to the results of our study. Similar to our study, age and gender had no relationship with hypercalciuria in this study. Mohkam et al. have assessed the effect of ceftriaxone on incidence of kidney stones in children. In their research, 284 children were studied. The patients were under treatment with ceftriaxone for 9 to 10 days. All patients underwent ultrasonography on the first or second day of admission which was repeated at the end of the treatment. In complicated cases, the ultrasonography was repeated after 3 months. The baseline ultrasonography was similar in all patients. In the 2nd ultrasonography, 4 out of 284 patients developed kidney stones. The patients who developed kidney stones in this study had similar Ca/Cr ratio in comparison to other patients (10). Age and gender had no role in urine Ca/Cr ratio. These findings were similar to our findings. Furthermore, Azita Fesharakinia et al. in 2013 studied 96 patients who were under treatment with ceftriaxone. In this study 6 patients developed kidney stones and 1 patient developed gallbladder stones. In this study, Ca/Cr ratio was similar in these patients before and after study in both groups (11). Age and gender had no role in development of kidney stones as shown in our study. In this study, urine Ca/Cr ratio was not measured.

4.2. Study limitations

Short duration of follow up in our patients limits the generalization of our findings. Ceftriaxone may have long-term complications in the urinary system which is not assessed in our study. Also, we have assessed only urine Ca/Cr ratio. Using ceftriaxone or ampicillin and cefotaxime may have other complications which are not assessed in our study. We have only assessed urine Ca/Cr ratio. It is not clear whether or not the increased levels of Ca/Cr ratio increase the risk of kidney stones.

5. Conclusions

Based on the results of our study, ceftriaxone is associated with higher levels of Ca/Cr ratio in comparison to ampicillin and cefotaxime in children with febrile bacterial infections. The results of similar studies are inconsistent and it's unclear whether or not the increased urine Ca/Cr ratio increases the risk of kidney stones. Despite this we recommend using alternative regimens of antibiotics instead of ceftriaxone when it is possible.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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