ORIGINAL ARTICLE

JIACM 2020; 21(3-4): 146-50

Occurrence and Natural Course of Ceftriaxone-associated Nephrolithiasis in Indian Children – A Prospective Observational Study

Dheeraj Bahl, Varsha Jayan***

Abstract

Objective: To study the occurrence and natural course of ceftriaxone-associated nephrolithiasis in Indian children.

Study design: Prospective observational study.

Participants: 153 children who received intravenous ceftriaxone during hospitalisation.

Intervention: A total of 153 children who received intravenous ceftriaxone during hospitalisation were enrolled in our study. Serial ultrasonography was performed to look for appearance and disappearance of renal calculi. Children who developed renal calculi were followed-up for symptoms of renal calculi.

Results: The incidence of nephrolithiasis after ceftriaxone therapy was found to be 1.3% (2 out of 153). The incidence of renal calculi was equal in both genders. In our study we did not find any significant relationship between occurrence of nephrolithiasis with age and dose of ceftriaxone. Size of renal calculi in both cases was almost similar, i.e., 2 mm and 3 mm. We observed that, in both cases renal calculi occurred after 7 days of ceftriaxone. Disappearance of renal calculi was seen after 8 weeks and 6 months of stopping ceftriaxone. No symptoms of renal colic were observed during follow-up in both cases.

Conclusion: Ceftriaxone associated nephrolithiasis is seen to be reversible. Creating awareness among surgeons can avoid unwanted surgery in such cases as these patients can be managed conservatively.

Introduction

Nephrolithiasis is one of the most commonly known ancient (since 4000 BC) ailment affecting the urinary tract of human beings. Approximately 12% of the global population is afflicted by nephrolithiasis at any time during their life span. The risk of developing urolithiasis in adults appears to be higher in the western world (5 - 9% in Europe, 12% in Canada, 13 - 15% in the USA) than in the eastern hemisphere (1 - 5%), although the highest risks have been reported in some Asian countries such as Saudi Arabia (20.1%). The incidences of urinary bladder stones is decreasing in developed countries but are frequent during the first years of life in various areas of Turkey, Iran, India, China, Indochina and Indonesia[1].

The various factors influencing the formation of nephrolithiasis include gender, dietary habits nutritional status, tropical regions – probably due to scant fluid intake and low urinary output[2]. Probably better modalities of diagnosis and treatment are also a contributing factor. In Indian population, approximately 12% are expected to have urinary stones, and out of these 50% may end up in renal failure[3].

Overview of risk factors

In children with nephrolithiasis, an underlying risk factor is identified in 75 to 85 per cent of affected children[8-12], e.g., urinary tract infection, and/or a structural renal or urinary tract abnormality[4-9].

Drug-induced nephrolithiasis is rarely described in children. The incriminated drugs are ceftriaxone, trimethoprim-sulfamethoxazole, topiramate, antiretroviral drugs (atazanavir, indinavir, sulfadiazine)[10].

Ceftriaxone is one of the third-generation parenteral bactericidal cephalosporin, is widely used across the world in the treatment of various infections in patients including children. On account of its long plasma half-life, it can be used as once-a-day dosage.

Schaad *et al* in 1988 for the first-time reported association of ceftriaxone and biliary pseudolithiasis[11]. Cochat *et al* in the year 1990 reported ceftriaxone-induced nephrolithiasis for the first-time and it was predominantly seen in cases of treatment of meningitis and diarrhoea who were put on ceftriaxone[12]. In both the conditions there was probably compromise of intravascular fluid.

Professor,**Post-Graduate Student, Department of Paediatrics, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.
Corresponding Author: Dr Varsha Jayan, Professor, Department of Paediatrics, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr Ram Manohar Lohia Hospital, Baba Kharak Singh Marg, New Delhi - 110 001. Tel: 9497273697, E-mail: varshajayan@yahoo.co.in.

Chutipongtanate *et al* showed that ceftriaxone at therapeutic levels could be crystallised with free calcium in the urine under physiologic conditions. He hypothesizes that tubular occlusion and crystal-cell adhesion may play an important role in the pathogenic mechanisms of ceftriaxone-induced nephrolithiasis[13].

The preparation used for the intravenous route is ceftriaxone disodium salt, which is poorly water-soluble[14]. Avci *et al* in 2003 suggested that ceftriaxone can bind with calcium ions, producing a precipitate that forms biliary sludge, also known as biliary pseudolithiasis. The same has also been observed in many studies since 1988[15].

Wang *et al* in 2017 observed that complications associated with ceftriaxone treatment, such as gallstonea and nephrolithiasis do happen[16] while Arvidsson *et al* elaborated that approximately 33 - 67% of the administered dose is eliminated through renal excretion, while 40% is secreted in the bile[17].

There is no information on urinary tract calculi as one of the side-effects of ceftriaxone in Indian children. Also, no study has been carried-out in ceftriaxone induced nephrolithiasis in India. In this light, the present study was performed to assess the incidence of nephrolithiasis and gallstones associated with ceftriaxone administration, possible correlation between ceftriaxone dosages, duration of treatment, weight of patient, diagnosis, BMI and age of the patient with nephrolithiasis, as well as any predisposing factors in Indian children on ceftriaxone.

Material and methods

This was a prospective observational study conducted after ethical clearance, in the department of Paediatrics and Radiodiagnosis in a tertiary care teaching hospital in New Delhi, India, from November 2017 to March 2019. Any child admitted to this hospital with suspected or definite bacterial infection was eligible for the study if the physician in charge of the case had decided to start ceftriaxone therapy. A total of 153 patients who received intravenous ceftriaxone (same dosage and brand) during hospitalisation were enrolled in our study. The clinical conditions for which ceftriaxone was given included – meningitis, infective diarrhoea, enteric fever, peritonitis, cellulitis, liver abscess, respiratory tract infections.

For each case, routine investigations including haemogram, LFT, KFT, urine analysis, urine culture before and after treatment, serum levels of calcium, urea, and creatinine, spot urine levels of calcium and creatinine were sent.

There was no fluid restriction and dehydration were monitored clinically and prevented.

Ultrasonography was done to assess renal, ureteric, and urinary bladder calculi, biliary sludge, cholelithiasis, and calculi size. USG was done on D0, D3, D7, D21 and further follow-up on D45, D60, till the findings disappeared. Ultrasonography on all the enrolled patients were done using the same equipment and the presence of nephrolithiasis was confirmed by two operators.

Criteria for positive renal calculi were bright echogenic foci with posterior acoustic shadowing while for gallstones presence of mobile, gravity dependent, echogenic material accompanied by clear acoustic shadowing and sludge was diagnosed when hyperechogenic bile showed no acoustic shadowing. Patients who developed renal calculi, biliary sludge/calculi were followed-up for symptoms of renal colic, acute cholecystitis like fever, vomiting, right hypochondrial pain. The respective days of appearance and disappearance of renal calculi, biliary sludge, cholelithiasis were noted. Persistence of either stone or sludge beyond 60 days was to be followed-up to 6 months or disappearance whichever is earlier. For each patient, we calculated the urine calcium: creatinine ratio before and after treatment. The means for the two-time points were compared to assess the effect of ceftriaxone on urinary calcium excretion.

Exclusion criteria were congenital renal malformations, deranged renal function, those who already had renal calculi, underlying metabolic disorder, deranged LFT, KFT, underlying haemolytic anaemias, malabsorption or any chronic disease patients on drugs, e.g., furosemide, octreotide. sulfonamides, topiramate, antiretroviral.

Statistical methods

Descriptive statistics was analysed with SPSS version 17.0 software. Continuous variables were presented as mean ± SD. Categorical variables was expressed as frequencies and percentages. The Pearson's chi-square test or the chi-square test of association was used to determine if there is a relationship between two categorical variables.

The P value less than 0.05 was considered to be statistically significant.

Results

Only 2 patients out of 153 (1.3 %) showed the occurrence of renal calculi. The sizes were 2 mm and 3 mm each. In both the cases, renal calculi appeared after D7 of starting the CTX respectively. There was no occurrence of ureteric and urinary bladder calculi. Both were located on upper pole of kidney and disappeared after 8 weeks and 6 months respectively.

Table I: Correlation between renal calculi and age.

Age (years)	Renal Calculi		Total	p - value
	No	Yes		
< 3	43 (97.7%)	1 (2.3%)	44	–
3 - 6	41 (100.0%)	0 (0.0%)	41	0.998
6 - 9	33 (100.0%)	0 (0.0%)	33	0.998
> 9	34 (97.1%)	1 (2.9%)	35	0.870
Total	151 (98.7%)	2 (1.3%)	153	–

That is, there is no relationship between renal calculi and age. The table reveals that the occurrence of renal calculi is almost the same in all age groups.

Table II: Correlation between renal calculi and weight.

Weight (kg)	Renal Calculi		Total	p - value
	No (%)	Yes (%)		
< 10	18 (100.0%)	0 (0.0%)	18	–
10 - 20	81 (98.8%)	1 (1.2%)	82	0.999
20 - 30	40 (97.6%)	1 (2.4%)	41	0.999
30 - 40	12 (100.0%)	0 (0.0%)	12	1.000
Total	151 (98.7%)	2 (1.3%)	153	–

There is no relationship between renal calculi and weight. The table reveals that the occurrence of renal calculi is almost the same in all weight groups.

Table III: Correlation between renal calculi and height.

Height (CM)	Renal Calculi		Total	p - value
	No	Yes		
< 75	14 (100.0%)	0 (0.0%)	14	—
75 - 100	39 (97.5%)	1 (2.5%)	40	0.999
100 - 125	60 (100.0%)	0 (0.0%)	60	1.000
> 125	38 (97.4%)	1 (2.6%)	39	0.999
Total	151 (98.7%)	2 (1.3%)	153	—

That is, there is no relationship between renal calculi and height. The table reveals that the renal calculi is almost same in all height groups. Also, no correlation between BMI and renal calculi was noted.

Table IV: Correlation between renal calculi and dose.

Renal calculi	Mean	SD	Median	Mean rank	p - value
No	1890	747.7	1700	76.96	0.930
Yes	2050	1344	2050	79.75	

The table reveals that the dose of ceftriaxone is higher but not significant in cases with renal calculi (2,050 mg) compared to the cases with no occurrence (1,700 mg). There is no relationship between renal calculi and dose.

Table V: Correlation between renal calculi and duration of ceftriaxone.

Duration of ceftriaxone (Days)	Renal Calculi		Total	p - value
	No	Yes		
< 7	73 (100.0%)	0 (0.0%)	73	–
7 - 14	64 (97.0%)	2 (3.0%)	66	0.997
> 14	14 (100.0%)	0 (0.0%)	14	1.000
Total	151 (98.7%)	2 (1.3%)	153	–

Here the p-values suggest that the relationship between renal calculi and duration of ceftriaxone is not significant.

Table VI: Use of ceftriaxone in various infections.

Diagnosis	Renal Calculi		Total	p - value
	No	Yes		
CNS disease	28 (100.0%)	0 (0.0%)	28	–
Cardiovascular disease	10 (100.0%)	0 (0.0%)	10	1.000
Pulmonary disease	37 (100.0%)	0 (0.0%)	37	1.000
Gastrointestinal disease	60 (98.4%)	1 (1.6%)	61	0.998
Rheumatological and haematological disorders	8 (100.0%)	0 (0.0%)	8	1.000
UTI	8 (88.9%)	1 (11.1%)	9	0.998
Total	151 (98.7%)	2 (1.3%)	153	–

Here the p-values suggest that the relationship between renal calculi and diagnosis is not significant. That is, there is no relationship between renal calculi and diagnosis. The table reveals that the renal calculi are almost same irrespective of diagnosis.

None of our patients showed a change in urinary excretion of calcium related to ceftriaxone therapy.

Discussion

The objective of our study was to study the occurrence of ceftriaxone-associated renal calculi and its correlation with dose, duration, weight, height, BMI, infection type, and gender. Only two out of 153 patients developed renal calculi (1.3%). The occurrence of renal calculi was equal in males and females. This was similar in the study by Avci *et al*[15] and Ghodsiyeh Azarkar *et al* (1.5%) in 2013[24]. But Fesharakinia *et al* reported a higher incidence of (6.3%)

and all were asymptomatic[23].

In contrast Acun *et al*, showed higher occurrence in females[25]. Mohkam *et al*, too observed the incidence at 1.4%[22].

Size of renal stone in our study was 2 - 3 mm, whereas Mohkam *et al* reported a calculi size of 15.5 mm, and interpolar sized 6.5 mm.

The urine of children has high concentration of citrate and magnesium which inhibit formation of crystal. This may be a reason of infrequent nephrolithiasis as compared with adults[18,19].

No age, gender, race is exempt as far as occurrence of nephrolithiasis is concerned, but the occurrence and recurrence are higher in males in the age of 20 - 49 years.

Gender preponderance of nephrolithiasis is not seen in paediatric age group. Several studies do show a slightly higher prevalence in boys[20]. But a study by Huang *et al* found in Taiwan, a slightly higher prevalence in female children (52% versus 48%)[21].

Our study is consistent with studies carried out by Mohkam *et al* and Avci *et al* as far as occurrence of nephrolithiasis is concerned[22,15]. However, Fesharakinia *et al* in 2013 observed that there was a significant correlation between male sex and ceftriaxone related asymptomatic nephrolithiasis[23]. It was also observed that occurrence of ceftriaxone-related small sized nephrolithiasis at 6.3% was higher and one (1%) patient had gallbladder stone was on lower as compared to other studies[23].

In our study the occurrence of renal calculi is almost same in all age groups. It is in accordance with a study by Avci *et al*, in which the comparison of the groups with and without nephrolithiasis revealed no significant differences with respect to age of the patient[15].

The size of renal calculi in both cases (both located on upper pole of kidney) in our study was also same ranging from 2 - 3 mm. In both cases, renal calculi appeared on D7 after starting ceftriaxone, and disappeared after 8 weeks and 6 months respectively.

According to our study, there is no relationship between renal calculi and dose of ceftriaxone, this was in contrast to the study by Avci *et al* in 2004, who found that children receiving a high-dose ceftriaxone (100 mg/kg/day) for the treatment of severe infections developed small renal stones in 7.8% of cases[15].

In our study, there is no relationship between renal calculi and duration of ceftriaxone. The occurrence of renal calculi is almost same in all duration groups. Our study is in agreement with the study done by Avci *et al* which elaborated that paediatric patients may develop small sized, asymptomatic renal stones during a 7-day course of ceftriaxone therapy[15]. Similar findings were noticed by Fesharakinia *et al* during a 2 - 6 day course of ceftriaxone therapy[23].

All the patients in our study remained asymptomatic and it is in accordance with a study conducted by Avci *et al* who also observed that the renal stones developed during a 7-day course of normal or high-doses of ceftriaxone therapy[15].

Prince JS, Senac *et al* and De Moor RA *et al* in their respective studies observed small size renal stones during a 2-6-day course of ceftriaxone and there was no significant difference in the two groups with and without nephrolithiasis as far as the dose and duration of therapy with ceftriaxone was concerned. Both the studies have reported high-doses of ceftriaxone and longer treatment time as risk factors for the development of nephrolithiasis[26,27].

It is important to understand occurrence of nephrolithiasis as complications of therapy with ceftriaxone as a self-limiting phenomenon. In contrast, confusion regarding these complications may lead to more invasive treatment such as surgery. There are many unreported incidences of surgical intervention in such ceftriaxone-induced pseudo-nephrolithiasis and pseudocholelithiasis. Awareness of ceftriaxone-induced pseudonephrolithiasis and cholelithiasis to the physician can certainly avert such eventualities and the patient can be managed conservatively.

Limitations

- In addition, the present study assessed the data from a single hospital; the findings of the research may not be more reliable than multicentre studies.
- Chemical composition of renal calculi could not be analysed due to non-availability of IR spectroscopy in our centre.
- It is difficult to make a proper conclusion in this study because of the small number of cases of nephrolithiasis arising out of ceftriaxone therapy.

Key messages

What is already known? Ceftriaxone is a broad-spectrum antibiotic that is widely used in the paediatric population. 60% of the drug is metabolised by the liver and the rest 40% by kidney. Cases of ceftriaxone-associated biliary cholelithiasis as well as nephrolithiasis have been reported. What does this study add? The occurrence of ceftriaxone-associated nephrolithiasis in our study has been found to be 1.3%. Our findings are similar to the previous studies

conducted on ceftriaxone-induced nephrolithiasis. But no study has been done in the Indian paediatric population. None of our patients developed symptoms of renal colic, and in both cases renal calculi resolved on follow-up. Hence, it is to be noted that ceftriaxone-associated nephrolithiasis can be managed conservatively without surgery.

References

1. Romero V, Akpinar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Reviews in Urology*, 2010; 12 (2-3): e86-e96.
2. Michelle hyperlink "https://www.ncbi.nlm.nih.gov/pubmed/?term=L%26%23x000f3%3Bpez%20M%5BAuthor%5D&cauthor=true&cauthor_uid=21476230"López and Bernd HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=Hoppe%20B%5BAuthor%5D&cauthor=true&cauthor_uid=21476230. *Hoppe,Pediatr Nephrol* 2010; 25 (1): 49-59.
3. Joseph KC, Bharat B, Parek H *et al*. Inhibition of growth of urinary type calcium hydrogen phosphate dihydrate crystals by tartaric acid and tamarind. *Current Science* 2005; 88: 232-1238.
4. Coward RJ, Peters CJ, Duffy PG *et al*. Epidemiology of paediatric renal stone disease in the UK. *Arch Dis Child* 2003; 88: 962.
5. Gearhart JP, Herzberg GZ, Jeffs RD. Childhood urolithiasis: experiences and advances. *Pediatrics* 1991; 87: 445.
6. Diamond DA. Clinical patterns of paediatric urolithiasis. *Br J Urol* 1991; 68: 195.
7. Perrone HC, dos Santos DR, Santos MV *et al*. Urolithiasis in childhood: metabolic evaluation. *Pediatr Nephrol* 1992; 6: 54.
8. Sarkissian A, Babloyan A, Arikyants N *et al*. Paediatric urolithiasis in Armenia: a study of 198 patients observed from 1991 to 1999. *Pediatr Nephrol* 2001; 16: 728-12.
9. Milliner DS, Murphy ME. Urolithiasis in paediatric patients. *Mayo Clin Proc* 1993; 68: 241.
10. Lozanovski VJ1, Gucev Z1, Avramoski VJ2 *et al*. *HIPPOKRATIA* 2011; 15 (2): 181-3.
11. Schaad UB, Wedgwood-Krucko J, Tschaeppeler H. Reversible ceftriaxone associated biliary pseudolithiasis in children. *Lancet* 1988; 2: 1411-3.
12. Cochat1 P, Cochat2 N, Jouvenet3 M *et al*. *Nephrol Dial Transplant* 1990: 5: 974-6.
13. Chutiponqtanate S, Thonqboonkerd V. Ceftriaxon crystallisation and its potential role in kidney stone formation. *Biochem Biophys Res Commun* 2011; 406 (3): 396-402.
14. Patel IH, Kaplan SA. Pharmacokinetics profile of ceftriaxone in man. *Am J Med* 1984; 77: 17-25.
15. Avci Z, Koktener A, Uras N *et al*. *Arch Dis Child* 2004; 89: 1069-72. doi: 10.1136/adc.2003.044156.
16. Wang S, Huang X, Xu Q. Research progress of mechanisms of ceftriaxone associated nephrolithiasis. *Mini Rev Med Chem* 2017; 17 (17): 1584-7.
17. Arvidsson A, Alván G, Angelin B *et al*. Ceftriaxone: renal and biliary excretion and effect on the colon microflora. *J Antimicrob Chemother* 1982; 10 (3): 207-15.
18. Miyake O, Yoshimura K, Tsujihata M *et al*. Possible causes for the low prevalence of paediatric urolithiasis. *Urology* 1999; 53: 1229.
19. Miyake O, Yoshimura K, Yoshioka T *et al*. High urinary excretion level of citrate and magnesium in children: potential aetiology for the reduced incidence of paediatric urolithiasis. *Urol Res* 1998; 26: 209.
20. Bush NC, Xu L, Brown BJ *et al*. Hospitalisations for paediatric stone disease in United States, 2002-2007. *J Urol* 2010; 183: 1151.
21. Huang WY, Chen YF, Chen SC *et al*. Paediatric urolithiasis in Taiwan: a nationwide study, 1997-2006. *Urology* 2012; 79: 1355.
22. Mohkam M, Karimi A, Gharib A *et al*. Ceftriaxone associated nephrolithiasis: a prospective study in 284 children. *Pediatr Nephrol* 2007; 22 (5): 690-94.
23. Azita HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=Fesharakinia%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24910741" HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=Fesharakinia%20A%5BAuthor%5D&cauthor=true&cauthor_uid=24910741"Fesharakinia, MD,[1,*] Ali-Reza HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=Ehsanbakhsh%20AR%5BAuthor%5D&cauthor=true&cauthor_uid=24910741"Ehsanbakhsh, MD,[2] and Nasrin Ghorashadizadeh, MD Ceftriaxone–Associated Nephrolithiasis in Children Iran J HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4025120/. *Pediatr* 2013; 23 (6): 643-7.
24. Ghodsiyeh Azarkar, Motahare Mahi Birjand, Alireza Ehsanbakhsh *et al*. *Drug, Healthcare and Patient Safety* 2018; 10: 103-8.
25. Acun C, Erdem LO, Söðüt *et al*. Gallbladder and urinary tract precipitationsassociated with ceftriaxone therapy in children: a prospectivestudy. *Ann Trop Paediatr* 2004; 24 (1): 25-31.
26. Prince JS, Senac MO. Ceftriaxone associated nephrolithiasis and biliary pseudolithiasis in a child. *Pediatr Radiol* 2003; 33 (9): 648-51.
27. De Moor RA, Egberts AC, Schroder CH. Ceftriaxone–associated nephrolithiasis and biliary pseudolithiasis. *Eur J Pediatr* 1999; 158 (12): 975-7.