Original Article

To compare the effectiveness of oral azithromycin versus intravenous ceftriaxone for treating uncomplicated enteric fever

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ABSTRACT

Objectives: To compare the clinical effectiveness of oral azithromycin versus intravenous (IV) ceftriaxone for treating uncomplicated enteric fever. **Methods:** Children aged 2-17 years with uncomplicated enteric fever and positive blood cultures for *Salmonella typhi* were included in the study. These were grouped as Group A (50 cases) and Group B (50 cases). Group A was given oral azithromycin 10 mg/kg/day once a day (azithromycin group) and Group B was given IV ceftriaxone 100 mg/kg/day in 2 divided doses (ceftriaxone group) for 6 and 7 days, respectively. Every day the child was examined, and the study results were assigned as a clinical and microbiological cure or failure. **Results:** A total of 100 patients in sex ratio of 1.2:1 (male:female) with uncomplicated enteric fever were enrolled in the study. Mean duration to become afebrile was less with azithromycin (2.72 days) as compared to ceftriaxone (5.52 days) treatment (p=0.000). 96% of the cases treated with azithromycin attained defervescence by the 5th day of treatment, but only 27% of cases treated with ceftriaxone attained defervescence by the 5th day of treatment. A clinical cure was earlier with azithromycin than with ceftriaxone treatment (p=0.027). Microbiological cure was achieved in 100% and 98% cases treated with azithromycin and ceftriaxone, respectively (p=0.5). **Conclusion:** Oral azithromycin was more efficacious in the treatment of uncomplicated enteric fever in children as compared to IV ceftriaxone.

Key words: *Azithromycin, Blood culture, Ceftriaxone, Defervescence, Enteric fever*

Enteric fever is a potentially fatal multisystem illness caused by *Salmonella typhi* or *Salmonella paratyphi* [1]. It occurs worldwide where water supply and sanitation are substandard [2]. Enteric fever is highly endemic in developing countries, especially in Asia and Africa, with documented high prevalence among children. It is estimated that more than 26.9 million enteric fever cases occur annually, of which 1% results in death [3,4].

The emergence of multidrug-resistant *S. typhi* has complicated therapy by limiting treatment options [5]. Fluoroquinolones have proven to be effective; however, their routine use in children is still restricted, and quinolone-resistant strains of *S. typhi* have begun to be reported [6,7]. Although ceftriaxone and other third-generation cephalosporins are still highly effective against *S. typhi*, they are considered to be less than ideal routine treatments [8-10]. In addition to the high cost and requirement of parenteral administration associated with ceftriaxone, *S. typhi* isolates resistant to this drug have begun to appear [11]. Therefore, other regimens are required for the treatment of enteric fever.

Azithromycin, a member of the macrolide class of antibiotics, possesses many characteristics for effective and convenient treatment of enteric fever including *in vitro* activity against many enteric pathogens, excellent penetration into most of the tissues, and achievement of concentrations in macrophages and neutrophils that are 100-fold higher than concentrations in serum [12-14]. In a study, 5 days after completion of 3-day course of azithromycin, neutrophil concentrations of the drug still exceeded the typical MIC for *S. typhi* by >20 times, whereas the drug was unmeasurable in the serum [13].

A recent Cochrane review reasonably concludes that clinical trials of enteric fever treatment over the last 40 years have not been ideal, and in particular, there has been a paucity of trials in children. From other studies, oral azithromycin administered once daily appears to be effective for the treatment of uncomplicated enteric fever in children. If these results are confirmed, this agent could be a convenient alternative for the treatment of enteric fever, especially in individuals in developing countries where medical resources are scarce. Hence, this study was conducted with the objective of studying the clinically effective drug (oral azithromycin versus intravenous (IV) ceftriaxone) for treating uncomplicated enteric fever.

MATERIALS AND METHODS

This prospective comparative study was conducted in Basaveshwara Medical College Hospital, Chitradurga, on

November 2014 to April 2016 after obtaining approval from Institutional Ethics Committee. A minimum sample size of 100 cases was required using an incidence of enteric fever as 78/2001 of total admissions in 6 months at our institution at a significance level of 0.05. Written informed consent of the parents/legal guardian was obtained before recruitment.

Children between 2 and 17 years of age admitted, with characteristic clinical features of uncomplicated enteric fever such as fever (temperature ≥38.5°C of at least 4 days), toxic appearance, abdominal tenderness, hepato or splenomegaly, coated tongue, diarrhea or constipation, and with positive blood culture for *S. typhi* were included in the study. These children were randomly divided into two groups to receive either azithromycin or ceftriaxone. Exclusion criteria were allergy to ceftriaxone or macrolides, major complications of enteric fever, inability to swallow oral medications, and treatment within past 4 days with an antibiotic that may be effective against *S. typhi*. Complicated enteric fever was diagnosed in the presence of enteric fever associated with intestinal perforation, hemorrhage, shock, encephalopathy, and pneumonia.

A pro forma was filled for each subject which included the demographic details of the patient, presenting complaints, associated symptoms, and documented temperature. Relevant blood investigations such as complete blood count, widal test (for ≥7 days fever), and blood culture were done on day 1 and 10 to correlate the treatment efficacy clinically and microbiologically using standard culture methods. Until blood culture reports available patients were treated symptomatically. The study groups received oral azithromycin 10 mg/kg/day OD for 6 days and IV ceftriaxone 100 mg/kg/day in 2 divided doses for 7 days [8,10].

Every day, each patient was evaluated and pro forma was updated with respect to temperature (axillary), appetite, hepatomegaly, splenomegaly, constipation/diarrhea, headache, and abdominal pain. Side effects of azithromycin and ceftriaxone were looked for and if they appear, the drug was changed to a safer one and the subject was excluded from the study. The patient was hospitalized for entire treatment period and next 3 days after therapy was completed. Any patient with fever or other symptoms suggestive of enteric fever 1 month after receiving therapy was evaluated and had a blood culture performed to determine whether there had been a relapse of enteric fever. Other samples were obtained for laboratory analysis as clinically indicated.

Definitions

Clinical cure was defined as the resolution of signs and symptoms by the end of 7 days of the treatment [1]. Defervescence/fever clearance was defined as the sustained period of 72 hours with axillary temperature of <37°C (98°F) [1]. Microbiological cure was defined as the sterile blood culture after treatment on day 10 of admission [1]. Microbiological failure was defined as an *S. typhi* positive blood culture on day 10. Clinical failure was defined as the persistence of ≥2 enteric fever related symptoms or signs present at study entry or as the development of an enteric fever related complications. Relapse was defined as recurrence of fever with signs or symptoms of enteric fever within 4 weeks of completion of therapy along with isolation of *S. typhi* or *S. paratyphi* from the blood.

Statistical methods used were contingency coefficient, Chi-square test, independent samples "t" test using SPSS for windows (version 16.0). $p<0.05$ was taken as statistically significant.

RESULTS

A total of 210 children with clinical features suggestive of enteric fever were screened for inclusion in the study. 100 patients in sex ratio of 1.2:1 (male:female) with clinical enteric fever and positive blood culture results were included in the study. The mean age of cases in azithromycin group was 8.5 ± 3.4 years and in ceftriaxone group was 7.3 ± 2.8 years. Male:female ratio was 1.02:1 and 1.3:1 in azithromycin and ceftriaxone group, respectively. The two groups were comparable with respect to demographic data, clinical presentations, and pretreatment laboratory evaluation.

In the current study blood culture, sampling was done before starting the first dose of antibiotic on day 1 of admission and another at 10th day of treatment, irrespective of the clinical outcome. Mean hemoglobin, total leukocyte count, and platelet counts were 12.2 g/dL, 6136/mm^3, and 2.16 lakh/mm^3, respectively, in azithromycin group while these were 11.16 g/dL, 5609/mm^3, and 3.8 lakh/mm^3, respectively, in ceftriaxone group. The antibiotic sensitivity pattern on blood culture showed more susceptibility of salmonella to cefixime, ceftriaxone, azithromycin and chloramphenicol. No isolate was found to be resistant to either ceftriaxone, azithromycin or ciprofloxacin, 1 isolate was resistant to trimethoprim-sulfamethoxazole, 2 were resistant to chloramphenicol, and 3 were resistant to ampicillin.

Both antibiotic therapies were highly effective (Table 1). Microbiological cure was achieved in 100% patient treated with azithromycin and in 98% of patients treated with ceftriaxone. The single patient who did not respond to therapy was clinically healthy and, after receiving a second course of antibiotic therapy (chloramphenicol), achieved complete cure, including sterilization of the blood. Mean time taken to become afebrile was 5.52 days and 2.72 days for ceftriaxone and azithromycin

Table 1: Response to treatment in both groups

Findings	Azithromycin group N=50	Ceftriaxone group N=50	p value
Clinical cure	49 (98%)	43 (86%)	0.027
Microbiological cure by day 10	100%	98%	0.5
Mean time to become afebrile (in days)	2.72	5.52	0.000
Anorexia responded on 3rd day	96%	76%	0.000
Relapse	0	6	

S: Significant, NS: Not significant, HS: Highly significant

groups, respectively. 96% of the cases treated with azithromycin, attained defervescence by the 5th day of treatment, but only 27% of cases treated with ceftriaxone attained defervescence by the 5th day of treatment. 88% defervescence was observed between 4 and 7 days of treatment with ceftriaxone.

After hospital discharge, 6 patients from the ceftriaxone group returned before their scheduled 1-month follow-up visit because of recurrence of enteric fever related symptoms. Cultures were performed, and 6 patients again had *S. typhi* recovered from their blood, which indicated a relapse of infection. All 6 patients were treated with a second course of antibiotics, with a resolution of their symptoms and sterile blood cultures after completion of the treatment regimen. None of the 6 isolates had developed resistance to any antibiotic tested including ceftriaxone. No relapses occurred in the azithromycin group. All subjects with abnormal results of pretreatment laboratory analysis had normal values at the end of therapy.

No serious adverse events occurred. Of the minor adverse events, gastrointestinal symptoms were the most common in both the groups. Vomiting occurred more frequently among patients treated with azithromycin (10 patients) than among those treated with ceftriaxone (6 patients) (p=0.2). Vomiting was typically mild and transient and did not require treatment or alteration of the antibiotic therapy. Diarrhea was the most common adverse event in patients treated with ceftriaxone, occurring in 16 patients, compared with 11 in azithromycin group. Diarrhea also did not require treatment or alteration of the antibiotic therapy regimen. Compliance with oral azithromycin was better compared to the IV ceftriaxone.

DISCUSSION

Our study demonstrated that azithromycin is highly effective for the treatment of uncomplicated enteric fever in children. In this study, clinical cure was obtained in 98% of patients treated with azithromycin, whereas in ceftriaxone group, it was 86%. Microbiological cure was achieved in all patients (100%) in azithromycin group, whereas it was 98% in ceftriaxone group. These findings were comparable with studies done by Wallace et al. [15] and Girgis et al. [16]. In our study, 12% of the subjects treated with ceftriaxone had relapses within 1 month of completion of therapy. These data were consistent with relapse rates of 5-15% in other trials of ceftriaxone therapy [17]. The concentration of azithromycin within cells and its secretion into the biliary tree, in conjunction with the long half-life of the drug, likely explain why relapses have not occurred with it when treating a principally intracellular infection such as enteric fever.

A study by Tribble et al. demonstrated that a 5-day course of azithromycin (20 mg/kg per day, with a maximum dose of 1000 mg/day) is effective against uncomplicated enteric fever in children and adolescents [18]. In our study, we used a low dose of azithromycin (10 mg/kg/day once a day) for 6 days and tried to compare with IV ceftriaxone. One of the reasons for this is to reduce the possible side effects related to the azithromycin usage [1]. The compliance was better with oral azithromycin due to once daily dosing as compared to the IV ceftriaxone which required frequent IV cannulation.

A report from Vietnam demonstrated that the duration of azithromycin therapy for uncomplicated enteric fever in adults could be decreased to 5 days [19]. The encouraging results from this trial prompted us to test whether a shorter treatment course could also be used in children and adolescents. 5 other studies have also demonstrated the effectiveness of azithromycin for the treatment of uncomplicated enteric fever in children, adolescents, and adults [16,18,20-22]. All these studies showed more than 90% clinical and microbiological cure without any serious adverse events or relapses.

Ceftriaxone is highly effective in the treatment of enteric fever but it is less than an ideal drug for its treatment. It shows a slow response with a mean time of 5-7 days or even longer to defervescence, which could be attributed to poor penetration capability of the drug into the cells, and thus difficult to eradicate the bacteria from the intracellular niche. Extended spectrum beta-lactamase (CTX-M-15 and SHV-12 ESBLs) and CMY-2-AmpC beta-lactamase producing *S. typhi* have been reported [23]. Rise in resistance to third or fourth generation cephalosporins has been observed in many studies.

On the other hand, azithromycin possesses many characteristics for effective and convenient treatment of uncomplicated enteric fever in children with efficacy rate of more than 95% [24,25]. However, treatment failure rates of 9.3% have been observed in earlier studies [26]. Two other studies have reported a clinical cure rate of only 82% and 92% [20,27]. The once-daily administration of azithromycin, combined with the short duration of therapy, may improve the compliance and ease the treatment of enteric fever. Future research directions include whether the duration of therapy can be further shortened to minimize costs and further simplifying treatment while maintaining efficacy. We recommend further large scale RCT trails to draw final inference.

CONCLUSION

Oral azithromycin (10 mg/kg/day once daily for 6 days) was more efficacious in the treatment of uncomplicated enteric fever in children and adolescents as compared to IV ceftriaxone (100 mg/kg/day for 7 days).

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