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Original Research Article

Intravenous Ciprofloxacin versus Oral Azithromycin in Treatment of Uncomplicated Typhoid Fever: A Randomized Controlled Trial

Bhuvanesh B T[1], Niveditha H V[2], Soumya D K[3], Uday K[4]

[1]Specialist in Pediatrics, CHC Doddakunche, Holenarasipur 573211india
[2]Assistant professor, Department of Pediatrics, Subbaiah institute of Medical Sciences
[3]SNCU specialist under NHM, GIMS Hospital Kalaburagi
[4]Assistant professor, Dept of Pediatrics, KIMS Koppal

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Corresponding Author: Dr. Bhuvanesh B T
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Abstract:

Objective: To compare efficacy of oral azithromycin with intravenous ciprofloxacin to treat uncomplicated typhoid fever.

Design: Randomized controlled trial.

Setting: Pediatric ward at Belagavi institute of medical sciences, Belagavi from January 2018-May 2019

Patients: 76 patients in the age group 2-18 years with positive WIDAL test were randomly allotted into one of the two groups of intervention as per computer generated random number table.

Intervention: One group (38 patients) received intravenous ciprofloxacin contained in 100 ml bottle (20 mg / kg / day in two divided doses) and another group (38 patients) received oral azithromycin (20 mg / kg / day in single dose). Patients monitored every 6th hourly for defervescence of fever and other symptoms.

Main Outcome Measures: Response to treatment (symptom control) with intravenous ciprofloxacin versus oral azithromycin. "Clinical cure" was considered as the resolution of symptoms by end of 5 days of treatment. "Clinical failure" was defined as persistence of 1 or more typhoid related symptoms.

Results: 89.47% (34 patients) responded in azithromycin group and 86.84% (33 patients) responded in ciprofloxacin group. Clinical cure was almost equal and difference was statistically insignificant (p-1.0). Mean duration taken for defervescence of fever was 42 hour in ciprofloxacin group compared to 48 hours in azithromycin group but difference was statistically insignificant (p-0.344)

Conclusion: Instead of intravenous ciprofloxacin, oral azithromycin for short duration, in single daily dose improves the patient compliance in treatment of typhoid fever.

Keywords: Typhoid fever; Azithromycin; ciprofloxacin; Defervescence; Clinical Cure; clinical failure.

Introduction

The typhoid fever caused by salmonella typhi remains a serious problem in developing countries like India. It is estimated that more than 26.9 million typhoid fever cases occurs annually out of which 1% result in death[1] These figures are representing the clinical syndrome rather than the culture proven typhoid fever cases. The typhoid infection is predominantly seen in school age. However, this infection is reported to be milder in infants and very young children.

There is a wide range of presentation with involvement of various organs [2]. The widespread emergence of multidrug-resistant S. typhi has necessitated the search for other therapeutic options. Fluoroquinolones have proven to be effective; however, quinolone-resistant strains of S. typhi have begun to be reported. Ceftriaxone, a third-generation cephalosporin, is highly effective against S. typhi and has become the standard of care for the treatment of typhoid fever in many parts of the world. However, because parenteral administration of ceftriaxone is required, the antibiotic is a less-than ideal treatment alternative.

The recent availability of the azalide class of antibiotics has provided another potential option for the treatment of typhoid fever. Azithromycin, the first azalide evaluated, has in vitro activity against many enteric intracellular pathogens, including S. typhi. Studies of human volunteers have shown that neutrophil concentrations of azithromycin are >100 times the serum concentration of the antibiotic. Five days after a 3-day course of azithromycin was completed, neutrophil concentrations of the drug still exceeded the typical MIC for S. typhi by >20 times, whereas the drug was unmeasurable in the serum.

These encouraging results led us to initiate a trial of azithromycin treatment in humans. Initially, azithromycin was demonstrated, in an open-labeled, nonrandomized trial, to be effective in the treatment of adults with uncomplicated typhoid fever. A subsequent randomized trial demonstrated that azithromycin was as effective asciprofloxacin for the treatment of uncomplicated typhoid fever in adults. The results of these studies prompted the present study of azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. All seven trials used a short-course azithromycin regimen (five to seven days). Two trials treated participants for five days, whereas the other five trials used a seven day regimen.

Thus a macrolide like Azithromycin given in a high dose for 7 days is the most affordable first line option for these infections in areas of endemicity against injectable ciprofloxacin and or hospitalization which could prove to be great economic drain and resource burden in a developing country like India.

Methods

Febrile children of age group 2-18 years ,admitted at pediatric ward of Belagavi institute of medical sciences over a period of one and half year from January 2018-May 2019 with positive widal test (H and O tire > or =160) were considered for study.

The patients with documented fever (rectal temperature >38.30c, oral > 37.80c or in axilla > 370C)[3] of more than 4 days with Symptoms like fever, anorexia, vomiting, diarrhea, headache, jaundice, abdominal pain, constipation [1] or signs like coated tongue, pallor, hepatomegaly, splenomegaly, icterus, and tenderness of abdomen [1] with or without blood culture growth of salmonella typhi. But with Single titre of O agglutinins > 1: 160 and H agglutinins >1:160 or four fold raising titres by tube agglutination type of widal test [4]were enrolled in the study. Patients who received antibiotics prior to enrollment and with culture proven urinary tract co infection were excluded.

Total 76 eligible patients were enrolled after obtaining informed written consent from either of parents. The study was double blinded and total study group was divided into 2 groups randomly by computer generated random number table. One group received intravenous ciprofloxacin contained in 100 ml bottle (20 mg / kg / day in two divided doses) [1] upto maximum 750 mg[5,6] and another group receive oral azithromycin (20 mg / kg / day in single dose)[1]upto maximum 500 mg / day[6]

Blinding was done by giving IV normal saline contained in 100 ml bottle (10 ml/kg/day) in group receiving Azithromycin and oral placebo(multivitamin tablet) in group receiving IV ciprofloxacin. Each group contained drug and placebo after masking the label of the drug and thus both groups of treatment appeared similar to patients.

Both the groups received symptomatic treatment (antipyretic, antiemetic, IV fluids) till either of blood culture or widal test became positive, after which antibiotics was also started. If symptoms including fever and signs were not controlled with either of drugs in 5 days [6] then it was considered as treatment failure. Then next line of drug given was IV ceftriaxone (75 mg / kg / day) in two divided dose [1].

During period of hospitalization, clinical examination of patient was performed daily based on a structured form. The vital parameters (including body temperature) measured 6 hourly. Response to treatment was defined as subsidence of symptoms (including fever) within 5 days of administering either of the drugs.

To all responders, corresponding drug was given for total duration of 7 days.

All non-responders were given IV ceftriaxone (75 mg/kg/day) for total duration of 7 days.

“Clinical cure” in this study was considered as the resolution of symptoms and signs by the end of 5 days of treatment. “Clinical failure” was defined as persistence of 1 or more of typhoid related symptoms which were present at the beginning of study in the subject, even after 5 days.

We included all the widal positive enteric fever cases over a period of one and half year after considering inclusion and exclusion criteria, thus total sample size obtained was 76, out of which 38 cases allotted for treatment with azithromycin and 38 cases for treatment with ciprofloxacin after randomization as per computer generated random number table.

Statistical analysis: Proportions were compared with the chi square test or the Fisher exact test. Fisher exact test was used for the outcome variable(proportion of clinical cure in both the groups)The mean duration of clinical response to treatment were compared between the two groups using non-parametric Mann whitney U test as the data was not normally distributed. A P value of <0.05 was considered as significant. Fig 1 depicts the study flow.

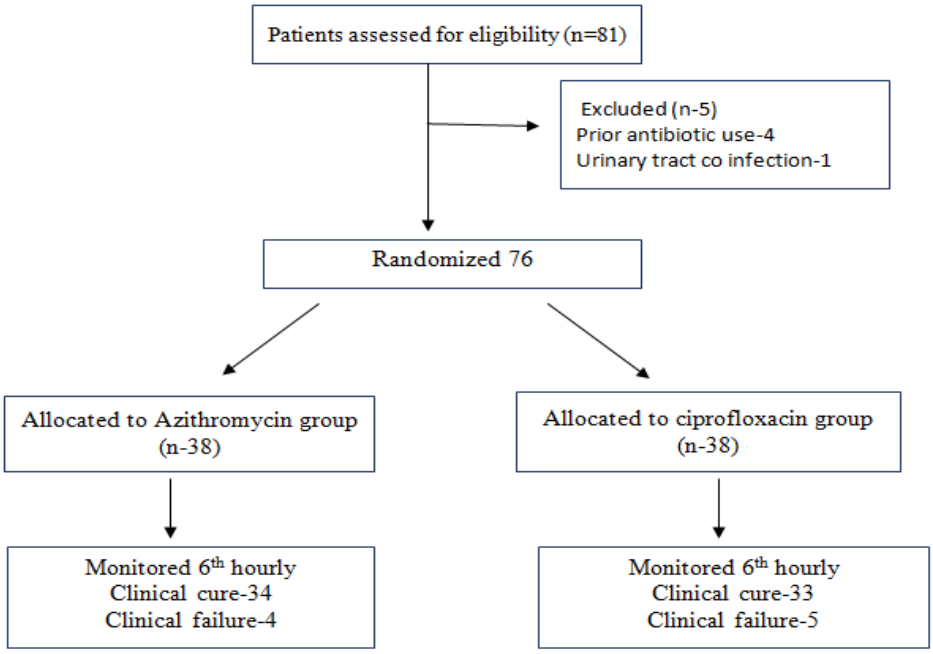

Figure: 1 Flow of participants in the study

Results

Cases were predominantly seen in the age group of 7-12 years (43 patients). Mean age of cases selected for azithromycin trial group was 9.4 years and for ciprofloxacin trial group was 8.3 years. Overall there was sex ratio (male: female) of 1.45:1 with ratio of 2.1:1 in azithromycin trial group and 1:1 for ciprofloxacin trial group.

Analysis of demographic characteristics revealed no statistically significant differences (p value for age comparison- 0.675 and for sex comparison-0.102) between patients treated with ciprofloxacin and those treated with azithromycin. Cases in both groups presented with fever as their main complaint and were present in all 100 % cases. Vomiting (44.74%) was the 2nd most common symptom noted in study subjects followed by pain abdomen (18.42%), loose stools (15.79%), cough (13.16%) and headache(2.63%).Symptom comparison between two groups depicted in Table I. Most common sign noted among study subjects was hepatomegaly (44.74%) followed by splenomegaly (15.79%), coated tongue (10.53%), and abdominal tenderness (5.26%) and rose spots (1.32%). Analysis of pretreatment laboratory results revealed no statistical significance between patients treated with azithromycin and those treated with ciprofloxacin. Most common lab abnormality seen was aneamia (cut off – age based normal value) and was seen in 28.95% of cases followed by leucocytosis (>11000/microlitre), relative lymphocytosis in 18.42% (>40%) and thrombocytopenia in 2.63% (<1.5 lakh/microlitre)

Our study included 76 patients of febrlile illness with WIDAL positive enteric fever. 67(88.16%) children in total attained clinical cure within 7 days, while 9(11.84%) failed to become so in 7 days. In the oral azithromycin group ,34(89.47%) children attained clinical cure in 7 days and 4(10.53%) failed to become so,in the Intravenous ciprofloxacin group,33(86.84%)children achieved clinical cure in 7 days and 5(13.16%) failed to do so, therefore difference in proportion of patients achieving clinical cure was not significant statistically (p-1.0)

The average defervescence time of 70.76±32 hours in oral azithromycin was longer than in intravenous ciprofloxacin (67.27±38 hours),however this was neither statistically significant (p-0.344) nor clinically relevant. Among responders, defervescence of fever occurred maximum within 96 hours in both azithromycin and ciprofloxacin groups.

Table 1: Analysis of Symptoms among Study Subjects

Symptom	Azithromycin Group	Ciprofloxacin Group	Total	P Value
Fever	38	38	76(100%)	1.0
Vomiting	13	21	34(44.74%)	0.065
Pain Abdomen	10	4	14(18.42%)	0.076
Loose Stools	4	8	12(15.79%)	0.208
Cough	2	8	10(13.16%)	0.042
Head Ache	1	1	2(2.63%)	1.0

Table 2: Comparison of Outcome of the Study

Outcome	Azithromycin Group	Ciprofloxacin Group	P Value
Clinical Cure	34	33	1.0
Clinical Failure	4	5	

Discussion

Enteric fever is a common illness of children and young adults thus having significant socioeconomic impact on the community. The industrialized and more prosperous countries have, to a greater extent controlled this illness by improving standards of public health; but the disease continues to be a major public health problem in less developed countries like India.

Thus in countries like India, where typhoid fever is highly endemic but have limited resources, the cost and compliance of treatment as well as safety and efficacy of the regime play an important role .In our study ,the two drugs compared were oral azithromycin and intravenous ciprofloxacin, both the treatment groups were successful without occurrence of complications during or after the treatment. Robert W Frenck Jr et al.[7] found that in vitro resistance to azithromycin did not correlate well with its in vivo effectiveness against typhoid fever. This is possibly because susceptibility testing is based on serum drug levels, whereas for typhoid fever, a major mechanism of action is thought to be intracellular killing, in which the azithromycin levels may be 100-fold greater than serum levels.[8,9,10]

A study by Tribble D et al. (1995), demonstrated that a 5-day course of azithromycin (a dosage of 20 mg/kg per day, with a maximum dose of 1000 mg/day) is effective against uncomplicated typhoid fever in children and adolescents [7]. Another study done by Anju Agarwal (2000) concluded that a short course of 6 days of Azithromycin is safe and effective in treating uncomplicated enteric fever [11].Study done by Bindu T Nair et al concluded that azithromycin is safe and effectice alternative to cephalosporins [12].The compliance will be better in azithromycin because of no need of cannulation and less frequent administration and similar results were found in studies done by Robert W Frenck Jr et al.[7,11]

A recent report from Vietnam demonstrated that the duration of azithromycin therapy for uncomplicated typhoid fever in adults could be decreased to 5 days[13]. The encouraging results from this trial prompted us to test whether a shorter treatment course could also be used in children and adolescents. Similar 5 other studies have demonstrated the effectiveness of azithromycin for the treatment of uncomplicated typhoid fever in children, adolescents, and adults in each of the studies, clinical and microbiological cure rates have exceeded 90% without any serious adverse events or relapses of typhoid fever.[8,9,10,14]

Conclusion

Our study showed no significant difference between the clinical responses of the two groups. the limitation of our study was the small size of sample. Further studies will be required to confirm that resistance, relapse and long term carriage will not be a problem with azithromycin. Some patients with typhoid fever are unable to swallow oral preparations or have vomiting either due to the medication or illness. This may also limit its use as an OPD treatment.

Azithromycin is much less expensive than intravenous ciprofloxacin or the third generation cephalosporins and also eliminates the need of hospital stay and thus seems to be an effective alternative. The once daily dose of azithromycin along with the short duration of therapy is convenient and would improve patient compliance. Thus, ease of treatment of typhoid fever would remain the greatest advantage.

1. What is Already Known?

Ceftriaxone is the standard of care for the treatment of typhoid fever. However, because of need for parenteral administration, it is a less-than ideal treatment.

2. What This Study Adds?

Once daily dose of oral Azithromycin for short duration seems to be an effective alternative with better compliance.

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