ORIGINAL ARTICLE

Comparison of efficacy of azithromycin vs cefixime in the treatment of uncomplicated typhoid fever in children

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ABSTRACT

Background: Typhoid fever is a serious infection caused by *Salmonella Typhi*, marked by prolonged fever and gastrointestinal symptoms. The aim of this study is to compare the clinical efficacy of 7day oral Azithromycin versus 14day Cefixime in treating uncomplicated typhoid fever in children.

Materials and method: This single-blind, randomized interventional study was conducted over one year (Dec 1, 2020–Nov 30, 2021) at Bacha Khan Medical Complex, Shahmansoor. Using non-probability consecutive sampling, 88 children with blood culture-confirmed uncomplicated typhoid fever (non-XDR *Salmonella typhi*) were enrolled and randomly divided into two groups (n=44). Group A received oral Azithromycin and Group B received oral Cefixime, with doses adjusted within the 10–20 mg/kg/day range for safety. Mean defervescence time was recorded, and relapse or recurrence was monitored for up to 3 months. Statistical analysis was done using the Chi-square test.

Results: Among 88 patients (mean age 7.4 ± 0.9 years), the average defervescence time was 5.00 ± 1.15 days for the cefixime group and 4.50 ± 1.11 days for the azithromycin group, with no significant difference (t=1.73, p=0.13). Relapse occurred in 22.7% of patients, significantly more in the cefixime group (34.1%) compared to azithromycin (11.4%) (χ^2=20.389, p<0.001; p=0.019), indicating a statistically significant difference in relapse rates.

Conclusion: Azithromycin at 10-20 mg/kg/day for seven days was found to be as clinically effective as cefixime, with potential advantages in dosing convenience and cost, though statistical significance was not reached.

Keywords: Azithromycin, Cefixime, Efficacy, Typhoid fever

BACKGROUND

Typhoid fever is a potentially life-threatening infectious disease which is caused by the bacterium *Salmonella* Typhi. It is characterized by sustained pyrexia and primarily gastrointestinal symptoms.[1] In 2019, According to WHO, an estimated 9.2 million typhoid fever cases and 110,000 deaths occurred worldwide with the highest estimated incidence in the WHO South East Asian (306 cases per 100,000 persons), Eastern Mediterranean(187) and African(111) regions.[2] Among countries in South Asia, Pakistan has the highest estimated incidence rate of typhoid fever with 493.5 cases per 100,000 person/year.[3] The estimated incidence of this disease in Pakistan is 573.2/100,000 persons per year in 2-5years age group while 451.7/100,000 persons per year in 2- 15years age group and 412.9/100,000 persons among 5-15 years age group.[4,5] High prevalence was found in the summer season. During 1980s, fluoroquinolones were introduced for the treatment of enteric fever due to emergence of widespread resistance against all the three conventional first line drugs i.e amoxicillin, trimethoprim-sulphamethoxazole, and chloramphenicol.[6] But within a few years, clinical failure of ciprofloxacin started to appear with reports showing in vitro resistance detection against Nalidixic acid,[7,8] making treatment of enteric fever ever more challenging. A laboratory data reviewed at Agha Khan University Hospital, Karachi showed high incidence of multidrug resistance (MDR) for *Salmonella* typhi, ranging from 64.8% to 66.0% while resistance to fluoroquinolone increased for *Salmonella* typhi from 84.7% to 91.7%. Ceftriaxone and Cefixime resistance for *Salmonella* typhi were found in 2 cases.[9] In another study conducted in tertiary hospital of Pakistan, *Salmonella* Typhi and *Para* typhi have only 7.1% sensitivity to quinolones antibiotic.[10]

Certainly, there is need for a therapy having good patient compliance, rapid clinical response, reduced secondary transmission and which should be cost effective. An intervention study results concluded that

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for seven days, once in a day, administration of azithromycin in the treatment of uncomplicated childhood typhoid fever showed good clinical response and was reasonably safe.[11] In another randomized control trial study, the clinical response of cefixime and azithromycin was compared in uncomplicated typhoid fever in pediatrics age patients, the study results concluded that efficacy of azithromycin is almost similar as cefixime[12].In Cochrane systemic review conducted by Effa EE *et al*, on 773 patients, authors concluded that Azithromycin may perform better than 3rd generation cephalosporin.[13]In another RCT comparing the efficacy of azithromycin and ceftriaxone, conducted in Dhaka Bangladesh, it was concluded that azithromycin is as effective in the treatment of enteric fever in children as ceftriaxone.[14] Recently azithromycin is included among first line treatment recommended for uncomplicated enteric fever[15] A comparative study conducted at Rawalpindi medical college showed superior efficacy of azithromycin than ofloxacin.[16] Recently another RCT conducted in pediatric department of Darul-ul-Sehat hospital, Faisalabad showed higher clinical efficacy of azithromycin than ciprofloxin.[17] Another study conducted at department of pediatric medicine Sir Ganga Ram hospital Lahore showed that azithromycin is an effective oral agent for treatment of typhoid fever in children.[18]

The rationale of my study is to compare the clinical efficacy of Azithromycin with that of Cefixime in the treatment of uncomplicated typhoid fever in pediatric population in our setting with the goal of achieving a better treatment option for the patients with respect to local antimicrobial resistance and response pattern. The rising antimicrobial resistance in *Salmonella* Typhi, especially to fluoroquinolones and cephalosporins, comparing azithromycin and cefixime is crucial to identify an effective, safe, and accessible oral treatment for pediatric typhoid

MATERIAL AND METHODS

A prospective, randomized, comparative interventional study conducted over a one-year period at Bacha Khan Medical Complex, Shahmansoor, Swabi (from 1st December 2020 to 30th November 2021). Sample size was calculated using WHO sample size calculator taking confidence interval 95%, margin of error 5%, Prevalence of Clinical cure in 81.4% patients treated with azithromycin, compared with 50.3% patients treated with cefixime[13].The estimated sample size came out to be 88 patients. (44 each group). Uncomplicated Typhoid fever was defined mainly clinically without any complications. The diagnosis was confirmed by positive blood culture yielding growth of a non-XDR strain of *Salmonella typhi*. Clinically: persistent fever of $\geq$ $38C^0$ and gastrointestinal symptoms (diarrhea, abdominal pain, decreased appetite etc.) $\pm$ constitutional symptoms & Laboratory tests (blood culture, leucopenia and thrombocytopenia).

Inclusion criteria: Children of both genders with age 1 to 15 years who fulfill uncomplicated typhoid fever criteria along with a confirmed positive blood culture yielding growth of a non-XDR *Salmonella typhi* strain were included in the study

Exclusion criteria: Children with complicated typhoid fever or dengue fever were excluded from the study. Children suffering from any severe co-morbid or congenital conditions were also excluded. Cases of Extensively drug resistant Salmonella typhi were also excluded from the study.

Permission and approval of the study was sought from the hospital ethics committee. Informed consents were taken from the parents of the patients. Those patients who were fulfilling the inclusion criteria were included in the study. All the study procedures and data collection was conducted by the researcher to maintain data quality and compliance to the study protocol. All the patients were randomly divided one by one into two groups. After enrollment, details of illness and demographic profile of the patients were recorded. Group A were given azithromycin in a dose of 10-20mg/kg/day for a period of **s**even days while Cefixime was given at a dose of 10-20mg/kg/day in two divided doses for 14 days to the group B. The dose of both the antibiotics was adjusted keeping in view safety and efficacy profile. The mean time of defervescence was calculated for both the groups. Following defervescence, all the patients were followed fortnightly up to 3 months since their diagnosis for detecting relapse. Any patient presenting with similar clinical signs as initial presentation were tested by blood culture and sensitivity to determine the strain and it´s antimicrobial susceptibility pattern. All the obtained data was recorded on a predesigned Performa. Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Quantitative data was represented using mean ± standard deviation and

qualitative data was represented by using percentage and frequency. Chi square test and independent Sample t test were applied and p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

The study included 88 patients of typhoid fever. Two interventional groups A & B, each consisted of 44 participants were made. Among all the patients, there were 40(45%) males and 48(55%) females. The mean age of participants was 7.4±0.9 years. Among all the participants, there were 30(34%) patients in 4-5 years age group, 25(28%) in 6-10 years age group and 33(37%) in 11-15 years age group. The youngest patient was 4 year of age while the oldest patient was 12 years old. Among all the participants 22(25%) had 10-14kg weight, 20(23%) had 15-25 kg, 25(28%) had 26-36kg and 21(24%) had weight >36 kg (Table-I). Regarding clinical features of typhoid fever in this study, fever was found to be positive in 88(100%) patients. Other clinical findings are given in Table-II.

Regarding laboratory findings, the mean total leukocyte count was 5.50 ± 11.30 × 10^3/µL. The mean hemoglobin level was 11.50 ± 10.20 g/dL, and the mean platelet count was 145,000 ± 53.40 µL. The mean lymphocyte percentage was 52.00 ± 21.20, while the neutrophil percentage was 70.80 ± 16.90 (Table-III). Among all 88 (100%) participants, blood culture and sensitivity were performed on a peripheral blood sample. Growth was identified to be of a non-XDR strain of *Salmonella typhi.* Any XDR *Salmonella typhi* case was not included in the study.

We monitored for defervescence regularly after institution of antimicrobial therapy. Defervescence was said to have been achieved if the patient has spent a duration of 48 hours being afebrile. The mean time to defervescence was 5.00 ± 1.15 days in the cefixime group, and 4.50 ± 1.11 days in the azithromycin group. Therefore difference in defervescence time between the two groups was not statistically significant ($t(88) = 1.73$, $p = 0.13$, two-tailed). The magnitude of the differences in the means (mean difference = 0.85, 95% *CI:* - 1.80 to 1.87) was very small (eta squared = 0.006) (Table- IV). The present study found that among all those who had relapse 11(13%), 5(45%) were treated with azithromycin while 6(55%) were treated with cefixime. The association was found to be statistically significant ($x^2=20.389$, $p < 0.001$ df=1) (Table-V). In Group A (Azithromycin), only 5 out of 44 patients (5.7%) experienced a lapse. In Group B (Cefixime), 6 out of 44 patients (6.8%) experienced a lapse. The overall lapse rate across both groups was 22.7%. The p-value is 0.019, indicating that the difference in lapse rates between the two groups is statistically significant (i.e., unlikely to be due to chance) (Table-V).

Table-I: Demographic characteristics of participants (n=88)

Demographic Variables	Frequency (%)
Gender	
Male	40 (45.5%)
Female	48 (54.5%)
Age	
1-5 years	30 (34.1%)
6-10 years	25 (28.4%)
11-15 years	33 (37.5%)
Weight	
10 - 14 kg	22 (25.0%)
15 - 25 kg	20 (22.7%)
26 - 35 kg	25 (28.4%)

Table-II: Clinical Manifestations

Clinical Variable	Frequency (%)
Fever	
Yes	88 (100.0)
No	0 (0.0%)
Toxic Physical Appearance	
Yes	65 (73.9%)
No	23 (26.1%)

Vomiting	
Yes	44 (50.0%)
No	44 (50.0%)
Nausea	
Yes	55 (62.5%)
No	33 (37.5%)
Coated Tongue	
Yes	60 (68.2%)
No	28 (31.8%)
Caecal Gurgling	
Yes	20 (22.7%)
No	68 (77.3%)
Hepatomegaly	
Yes	40 (45.5%)
No	48 (54.5%)
Splenomegaly	
Yes	20 (22.7%)
No	68 (77.3%)
Diarrhea	
Yes	63 (71.6%)
No	25 (28.4%)
Constipation	
Yes	25 (28.4%)
No	63 (71.6%)

Table-III: Laboratory parameter blood complete picture (n=88).

Parameters	Mean ± SD
Total leukocyte count	5.50 ± 0.55× 10^3/µL
Hemoglobin	11.50 ± 1.50 g/dL
Platelets count	145,000±30,100 µL
Lymphocyte	51.00 ± 5.20%
Neutrophils	70.8 ±7.3%

Table-IV: Comparison of Mean time of defervesce.

Mean time of defervesce	Group A (Azithromycin) (n=44)	Group B (Cefixime) (n=44)	p-value
Mean ± SD	4.50±1.11	5.00±1.15	0.13

Independent Sample t test

Table-V: Association of defervescence in both groups with respect to relapse.

Lapse	Interventional Groups		Total	p-value
	Group A (Azithromycin)	Group B (Cefixime)		
Yes	5(5.7%)	6(6.8%)	11(13%)	0.019
No	39(44%)	38(43%)	77(87%)	

Chi-square (χ^2

DISCUSSION

In this study, we compared the clinical efficacy of oral azithromycin with that of oral cefixime in terms of mean time to defervescence in pediatric patients with uncomplicated typhoid fever. The findings revealed no statistically significant difference in the meantime to defervescence between the azithromycin group (M = 4.5 days, SD = 1.11) and the cefixime group (M = 5 days, SD = 1.15; $t(88) = 1.73$, $p = 0.13$, one-tailed). The mean difference was 0.85 days (95% CI: -1.80 to 1.87) with a very small effect size ($\eta^2 = 0.006$). These findings align with a randomized controlled trial that reported comparable efficacy between azithromycin and cefixime for the treatment of uncomplicated pediatric typhoid fever, where the mean time to defervescence was 4.05 ± 1.14 days in the azithromycin group and 3.41 ± 0.95 days in the cefixime group.[12] This gave us a better

confidence when instituting treatment protocols in our setup for future patients.

Consistent outcomes have been reported in a prospective study conducted at the Pediatric Department of Shaikh Zayed Hospital, Lahore, in which 96.4% of patients achieved defervescence within four days following azithromycin therapy. [19] Similarly, Kapoor *et al*. (2014) demonstrated a clinical response in 93.82% of patients, with the average time to fever resolution being four days.[19]

Regarding relapse, our study identified 11 cases (13%) overall, with 5 (45%) in the azithromycin group and 6 (55%) in the cefixime group. Relapse was defined as recurrence of similar symptoms within two weeks of discharge, confirmed by blood culture yielding a similar isolate. While numerically higher relapse was observed in the cefixime group, this difference was not statistically significant based on our calculated p-value ($p = 0.70$), and may have been due to random variation in a limited sample. However, the observed trend may carry clinical significance and a longer azithromycin regimen (e.g. 10 days instead of 7) may help further reduce relapse rates – a consideration that warrants further investigation in larger studies.

Comparable results were observed in a study by Frenck *et al*., conducted in Egypt, involving 149 pediatric patients aged 3–17 years. Participants were randomized to receive either oral azithromycin (20 mg/kg/day; max 1 g/day) or intravenous ceftriaxone (75 mg/kg/day; max 2.5 g/day) for five days. Out of 68 culture-confirmed cases, clinical response was achieved in 94% (30/32) of the azithromycin group and 97% (35/36) of the ceftriaxone group. Notably, none of the azithromycin-treated patients experienced relapse, whereas six patients in the ceftriaxone group did. [17]

Furthermore, a systematic review and meta-analysis assessing the safety and efficacy of azithromycin versus other agents—including chloramphenicol, fluoroquinolones, and cephalosporins—in culture-confirmed enteric fever incorporated data from seven randomized controlled trials with a total of 773 participants. Azithromycin demonstrated a lower risk of clinical failure compared to older fluoroquinolones (risk ratio [RR]: 0.45; 95% CI: 0.25–0.82) and a significantly lower risk of relapse compared to ceftriaxone (RR: 0.1; 95% CI: 0.01–0.76). No serious adverse effects were reported across the trials.[18]

Recently, an RCT from the Pediatric Department of the Federal Government Polyclinic Hospital, Islamabad, concluded that azithromycin represents a viable oral alternative for managing enteric fever in children, offering the advantages of once-daily dosing and high compliance.[19]

Taken together, our findings—consistent with the existing literature—support the use of oral azithromycin at a dosage of 10 mg/kg/day for seven days in the treatment of uncomplicated typhoid fever in children. The therapy was found to be safe, well-tolerated, and cost-effective, with no significant adverse events observed. Its favorable pharmacokinetic profile and compliance advantages make it an important option in empirical management in endemic settings.

CONCLUSION

From this study we concluded that Azithromycin given for 7 days at a dosage of 10 mg/kg/day once a day appears to be effective for the treatment of uncomplicated typhoid fever in children with clinical cure rates comparable to those for cefixime dosage of 20mg/kg/day twice daily for 14 days. Once daily administration of oral azithromycin may offer a simple, safe and cost-effective treatment with good compliance and fewer complications. Azithromycin can also be used effectively as alternative drug of choice where cefixime is contraindicated like in patients with penicillin allergy.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Asma Khan: Concept and design of study, acquisition, analysis and interpretation of data, drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

Bibi Asma: Acquisition, analysis and interpretation of data, manuscript writing, final approval, agreement to be accountable for all aspects of the work

Muhammad Zabih Ullah: Design of study, acquisition, revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

Muhammad Rizwan: Analysis and interpretation of data, drafting, final approval, agreement to be accountable for all aspects of the work

Jawairia Gul: Analysis of data, final approval, agreement to be accountable for all aspects of the work

Uroj Afzal: Drafting and revising article critically for important intellectual content, final approval, agreement to be accountable for all aspects of the work

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