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Comparison of Efficacy of Azithromycin with Ciprofloxacin in the Treatment of Uncomplicated Enteric Fever in Children

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Abstract

Objective: To compare the effectiveness of azithromycin to ciprofloxacin in the management of uncomplicated enteric fever in children between 6-12 years of age in the paediatrics department of Pakistan Atomic Energy Commission (PAEC) General Hospital.

Methods: It was a randomized control trial study, conducted at the Department of Pediatrics, PAEC General Hospital, Islamabad from 30-01-21 to 30-07-22. Data from 196 children with signs and symptoms of uncomplicated enteric fever was collected after obtaining verbal consent from their parents. Demographic information of the patients along with a short medical history were noted in pre-designed forms.

Results: Mean age, treatment time, body weight and defervescence time in the azithromycin group were 9.21±2.24 years, 5.87±1.78 days, 28.3±4.54 kg and 49.8±10.21 hours, respectively. Similarly, age, treatment duration, body weight and defervescence time in the ciprofloxacin group were 9.48±2.41 years, 6.41±1.14 days, 26.9±4.89 kg and 53.7±12.25 hours, respectively. The observed efficacy was 92 (93.9%) and 74 (75.5%) in the azithromycin and ciprofloxacin groups, respectively.

Conclusion: Azithromycin is an efficient outdoor patient treatment choice for children with uncomplicated typhoid fever and needs to be widely utilized in high-risk fluoroquinolone-resistant countries.

Keywords: Multi-Drug Resistance; Salmonella Typhi; Azithromycin; Ciprofloxacin.

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1. Introduction

Enteric fever is a potentially fatal multisystemic illness resulting from Salmonella enterica serovar typhi.[1] It is a fatal infectious illness that lasts for weeks having prolonged morbidity, if left untreated. Increasing antimicrobial resistance and indoor treatment in hospitals are other issues related to typhoid fever.[2] There are roughly 26.9 million instances of typhoid fever revealed every year leading to more than 269,000 deaths.[3] The public health burden of typhoid fever in India is extremely high. A population-based study in New Delhi observed that the frequency of typhoid was 2,730 per 100,000 in the 0-4 age group and 1,170 per 100,000 in the 5-19 age group.[4] Infection most often happens in low and middle-salary nations where sanitation and safe water supply frameworks are poor. However, with the emergence of antimicrobial resistance and an increase in international travel, this has now become a global threat.[5] Enteric fever happens primarily in youngsters between 5-19 years old, while in certain areas it is normal in children less than 5 years of age.[6]

As fluoroquinolone resistance has become a concern, the first-line treatment for typhoid fever has shifted towards third-generation cephalosporins like ceftriaxone and cefixime.[2] During 2016, an outbreak involving six extensively drug-resistant (XDR) S Typhi strains, resistant even to cephalosporins, was documented. Unfortunately, these medications were both costly and inaccessible in low-resource nations.[7] The emergence of extensively drug-resistant (XDR) strains underscored the critical need for alternative antibiotics to effectively combat this fever.[8] Azithromycin has emerged as the final oral treatment alternative to fluoroquinolones and cephalosporins. Its sensitivity, efficacy, high intracellular concentration, favourable clinical response, availability, and affordability have led to widespread use as an effective treatment for uncomplicated typhoid fever in both adults and children aged 9-10. With a treatment success rate of 90.7% and a failure rate of 9.3%, it has demonstrated notable effectiveness.[9]

The typical scaling pattern for typhoid fever is that the temperature rises by about 20°F at night and drops by about 10°F in the morning, so plateaus between 102 and 104°F rarely rise after 5 days.[10] But this trapezoid style is uncommon in children. Investigations have shown that 60% of patients have persistent fever with intermittent, mild or unstable resting fever.[11]

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There is a debate in the literature regarding the effectiveness of antibiotics in treating typhoid fever. Therefore, this research was carried out to evaluate the efficacy of azithromycin relative to ciprofloxacin in the treatment of children with uncomplicated typhoid fever at the Pediatrics Department of PAEC General Hospital. The rationale of the research is to find the effectiveness of azithromycin and ciprofloxacin in S Typhi strains. Comparing efficacy and emphasizing the 7 importance of one drug over another will help society to reduce the burden of disease in controlling enteric fever and thereby mortality. Moreover, this study will encourage researchers and Government authorities to visualize the aspects of disease on a wider scale. This study will provide baseline data on antibiotics to determine the best treatment options for uncomplicated enteric fever. This study is the first of its kind in this area and has never been done before in this hospital. This research will add something new to the existing data and knowledge on the treatment of typhoid fever in children.

2. Materials & Methods

Study design: Randomized control trial. Study setting: Department of Pediatrics, PAEC General Hospital, Islamabad. The study was conducted from 30-01-21 till 30-07-21. The sample size was calculated by using the WHO calculator, a sample size of 196 cases was selected and divided into group I = Azithromycin group and group II = Ciprofloxacin.[6,10] The sampling technique was Non-probability consecutive sampling. This study included children aged 6-12 with enteric fever symptoms, positive typhoid & blood culture, normal chest X-ray, urine test, and negative MP smear. Their CBC showed neutropenia, thrombocytopenia, sometimes pancytopenia, and elevated CRP, supporting the diagnosis of enteric fever and children with complicated typhoid and hypersensitivity to azithromycin or ciprofloxacin were excluded.

After obtaining verbal consent from the parents of patients, demographic data, including history was noted on a proforma. Study participants were divided, one group of patients was treated with azithromycin at a dose of 20 mg/kg/day for 7 days and the second group was treated with ciprofloxacin at a dose of 15 mg/kg/day in 2 divided doses for 7 days. After seven days of treatment, patients were reassessed with reports of typhoid, blood culture, CBC, CRP, relief of symptoms, any complications, relapse, adverse drug reaction, fever clearance time, and duration of treatment to see the effectiveness of the drug. All details findings of the treatment and results of follow-up investigations were documented, and the efficacy of drugs was determined.

The data was analyzed with SPSS. The quantitative variables (like age, weight, duration of treatment, defervescence time) were analyzed as mean±SD. The qualitative variables (such as gender of patients, and efficacy of both treatment groups) were analyzed as frequency and percentage. A chi-square test was applied to compare the efficacy of both treatment groups. A p-value of <0.05 was considered significant.

3. Results

The study population had similar age distributions, indicating comparable age demographics. The azithromycin group had a slightly shorter average treatment duration compared to the ciprofloxacin group. Both groups had similar weight ranges, suggesting that weight was not a differentiating factor between the two groups. The azithromycin group achieved defervescence (fever reduction) faster on average than the ciprofloxacin group. (Table 1)

Table 1: Descriptive statistics of the study population (n=98)

Variable	Mean ± SD	Range
Age azithromycin group (years)	9.21±2.24	6-12
Age ciprofloxacin group (years)	9.48±2.41	6-12
Duration of treatment in azithromycin group (days)	5.87±1.78	4-10
Duration of treatment in the ciprofloxacin group (days)	6.41±1.14	4-10
Weight azithromycin group (kg)	28.3±4.54	20-40
Weight ciprofloxacin group (kg)	26.9±4.89	20-40
Defervescence time azithromycin group (hours)	49.8±10.21	36-64
Defervescence time ciprofloxacin group (hours)	53.7±12.25	36-64

The azithromycin group had a higher percentage of females, whereas the ciprofloxacin group had more males. Both groups predominantly experienced fevers for 7 days or less. Additionally, a greater proportion of patients in the azithromycin group referenced within 48 hours compared to those in the ciprofloxacin group, suggesting that azithromycin may lead to a faster clinical improvement. Overall, azithromycin demonstrated higher efficacy in reducing fever duration and achieving quicker defervescence, despite differences in gender distribution between the groups. Table 2

The Azithromycin group had a higher efficacy compared to ciprofloxacin.

Table 1: Frequency distribution of gender, duration of fever, defervescence time gender distribution in azithromycin (98) versus ciprofloxacin group (98) for treatment of uncomplicated typhoid fever

Variables	Azithromycin group	Ciprofloxacin group
Gender		
Male	35 (35.7%)	57 (58.2%)
Female	63 (64.3%)	41 (41.8%)
Duration of fever		
≤7 days	62 (63.3%)	66 (67.3%)
>7 days	36 (36.7%)	32 (32.7%)
Defervescence time		
≤48 hours	37 (37.8%)	30 (30.6%)
>48 hours	61 (62.2%)	68 (69.4%)

(P<0.05) Post-stratification data revealed azithromycin to be more effective than ciprofloxacin in reducing fever within 7 days, with a statistically significant advantage. For fevers lasting longer than 7 days, both antibiotics were highly effective, with azithromycin showing a slight edge.

Table 3: Efficacy of azithromycin (98) and ciprofloxacin (98) in the study population

Groups	Efficacy (n=196)		P-value
	Yes	No	
Azithromycin group	92 (93.9%)	06 (6.1%)	**0.01***
Ciprofloxacin group	74 (75.5%)	24 (24.5%)	

**p value was significant*

Table 4: Stratification of Duration of fever and Defervescence time for efficacy of azithromycin and ciprofloxacin in respected groups

Variables	azithromycin group		ciprofloxacin group		P value
	Yes	No	Yes	No	
Defervescence time					
≤ 48 hours	34 (91.9%)	03 (8.1%)	23 (76.7 %)	07 (23.3%)	0.08
> 48 hours	58 (95.1%)	03 (4.9%)	51 (75%)	17 (25%)	0.01*
Duration of fever					
≤ 7 days	59 (95.2%)	03 (4.8%)	46 (69.7 %)	20 (30.3%)	0.01*
> 7 days	33 (91.7%)	03 (8.3%)	28 (87.5 %)	04 (12.5%)	0.57

When considering defervescence time, azithromycin again showed greater efficacy in achieving fever reduction within 48 hours, though this difference was not statistically significant. However, for defervescence times exceeding 48 hours, azithromycin's superiority was statistically significant. Overall, azithromycin consistently demonstrated higher efficacy in both reducing fever duration and achieving quicker defervescence compared to ciprofloxacin. (Tables 3 and 4).

4. Discussion

Typhoid fever is a significant worldwide human health issue in low-and middle-earning nations. The emergence of widespread antibiotic resistance complicates the treatment of typhoid fever. Azithromycin is one of the few reliable oral antibiotic options currently available for the treatment of typhoid, even though issues remain about changes in treatment response and rising resistance. Compared to ciprofloxacin, we used a human Salmonella infection model to recognize the treatment response of azithromycin in a better way. We show that azithromycin is effective in the treatment of typhoid in the model. Nevertheless, when compared to ciprofloxacin, azithromycin treatment led to prolonged duration of bacteremia and fever clearance times (>37.5°C). Our investigation delved into the pharmacokinetic profiles of both azithromycin and ciprofloxacin in our model, aiming to refine dosing strategies for optimal efficacy.[12]

A study involving 149 children and adolescents aged 3 to 17 years with clinical typhoid fever compared oral azithromycin (20 mg/kg daily; maximum dose, 1000 mg/day) to intravenous ceftriaxone (75 mg/day; maximum treatment dose, 2.5 g/day) administered daily for 5 days. Blood and stool samples were collected before treatment and on days 4 and 8 of therapy for culture. The final analysis required isolation of Salmonella enterica serovar typhi or Salmonella enterica paratyphi. Salmonella typhi was identified in 68 patients, with 32 receiving azithromycin. In the azithromycin group, 30 out of 32 patients (94%) were cured, compared to 35 out of 36 patients (97%) in the ceftriaxone group (P = NS). The azithromycin group had a longer mean time to bacteremia clearance than the ceftriaxone group. No recurrences were observed in the azithromycin-treated patients, while 6 patients receiving ceftriaxone experienced recurrence. The study concluded that a 5-day course of azithromycin was an effective treatment for uncomplicated typhoid fever in children and adolescents.[13]

An open-label, non-comparative study was conducted involving 117 children aged 2 to 12 years to evaluate the efficacy and safety of azithromycin (20 mg/kg/day for six days) in treating uncomplicated typhoid fever. Among the patients diagnosed clinically with typhoid fever, 109 (93.1%) completed the study. The mean duration of fever at presentation was 9.1 (SD 4.5) days. 102 (93.5%) patients were clinically cured and seven discontinued the study due to clinical deterioration. The mean number of days to respond was 3.45±1.97. The positive rate of Salmonella typhi in BACTEC blood culture was 17/109 (15.5%), and all of them achieved bacteriological cure. No severe side effects were monitored. In 95% of the cases, global health was good as evaluated by the investigators and subjects that were carried out at the end of the treatment. Azithromycin was found safe and effective in the treatment of uncomplicated typhoid fever.[14]

A total of 7 randomized controlled trials that involved 773 patients in the study met with inclusion criteria. Compared to previous fluoroquinolones, azithromycin was found to be slightly better at reducing the possibility of CF risks with a recurrence risk of 0.46 (95% CI 0.25-0.82), while compared with ceftriaxone, considerably reduced risk of recurrence 0.1 (95% CI 0.01-0.76) was observed. Serious adverse events were not reported in any of the studies. Azithromycin may be recommended as a second-line medicine for multidrug-resistant typhoid fever. However, a large study of patients in the pediatric age group is advised to draw firm conclusions.[15]

5. Conclusion

Azithromycin is an effective choice for the outdoor treatment of children with uncomplicated enteric fever and must be employed in countries with higher rates of resistance to fluoroquinolones. A high starting dose of azithromycin should be considered because in most cases it results in intracellular concentrations above the minimum inhibitory concentration (MIC) within the first 24 hours of therapy. Due to the growing resistance to fluoroquinolones and the prevalence of susceptibility to conventional preferred antibiotics, more research is needed to evaluate new treatment options, such as suitable azithromycin doses; new antimicrobial agents; antibiotic cycling; combinations in children therapy and treatment choices. To reduce the prevalence of antibiotic-resistant Salmonella typhi in children and improve their health, it is recommended to use TCVs by WHO guidelines, before evaluating new therapeutic strategies

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