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The Effectiveness of Azithromycin versus Cefixime in the Treatment of Typhoid Fever in Children

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ABSTRACT

Typhoid fever is brought on by the Salmonella Typhibacteria. Typhoid fever can present with a wide range of clinical symptoms, making diagnosis difficult. Salmonella Typhi isa bacterium that spreads quickly in unsanitary environments. In addition, this disease is more prevalent in places with inadequate hygienic conditions,economically unsustainable poor people, and rural areas with a lack of safe drinking water supply are at high risk ofdeveloping typhoid fever. **Objective:** To compare the results of azithromycin versus cefixime in the treatment of typhoid fever in children. **Methods:** A clinical/Quasi-Experimental study was conducted in the pediatric ward, Liaquat University HospitalJamshoro/Hyderabad by convenience sampling technique within the time frame of six months.SPSS Version 26.0 was employed to analyze the data,by using chi square test. **Results:** Out of 270 subjects, Individuals of age group (2-5 years) were more affected (53.4%). The male population was more affected (57.8%). Signs and symptoms like fever, abdominal pain, diarrhea and constipation were observed and calculated in this study.Clinical cure occurred in 110 (81.4%) of 135 patients treated with azithromycin, compared with 68(50.3%) of 135 patients treated with cefixime (p-value=<0.001). **Conclusions:** It was concluded that everyday taking of oral azithromycin may present a plain cure for typhoid fever brought on by drug-resistant or susceptible strains of Salmonella Typhi, which makes it potentially useful in places with limited access to healthcare services. Most of the children aged between 2 to 5 years with male predominance were affected.

INTRODUCTION

The major health threat is typhoid fever,especially for children[1]. Salmonella Typhibacteria, which causes typhoid, spreads quickly in unsanitary environments [2]. The prevalence of this disease is highest in places with inadequate sanitation. Typhoid Fever is a significant cause ofglobal mortality and morbidity, yet it has a high incidence in developing countries.According to estimates, there are 11–21 million cases of typhoid fever worldwide each year, with 1,20,000–1,60,000 deaths [3, 4].Before, there were about 6,00,000 deaths and 16 million cases, but the fatality rate had dropped. Ninety-three percent of cases worldwide are reported prevalence of typhoidfeverin various socio-demographicgroups in southeastAsia [5]. Pakistan is a developing country with a high rate of typhoid disease. Pupils older than five years have the majority of difficulties, with only one-third of patients experiencing intestinal fever. Overcrowding, bad laundry, and low personal well-being, goods, the use of waterwithout heating, meat sharing, beverages of ice cream, lower socioeconomic class,poor sanitation in homes are all elements that present to the development of typhoid andparatyphoidfever [6-8]. It affects approximately 21 million people worldwide each year, with the majority of cases occurring in South Asia.According to the World Health Organization(WHO), there have been between 11 and 21 million cases of typhoid fever globally, with a resulting mortality toll of between 1,20,000 and 1,60,000 [9-11].The health authorities in Pakistan have confirmed that between

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2016 and 2020, there were approximately 22,354 cases of typhoid fever, and 15,717 cases were widespread drug-resistant cases that camefromdiverse parts of Sindh [12-15].Typhoid fever is often spread by contaminated water, during the summer season and the rainy season.A derivative of the fundamental macrolide, azithromycin exhibits superior anti-gram-negative bacterial action compared to erythromycin. Cefixime is a third-generation oralcephalosporin using a spectrum related to other third-generation cephalosporin[16-17].

This study aims to analyze the efficacy of azithromycin, a newmacrolide,compared to that of cefixime, as a first-line drug for thetherapy of uncomplicatedtyphoidfeverin children.

METHODS

A clinical Quasi-Experimental study was conducted in the pediatric ward, Liaquat University Hospital Jamshoro Hyderabad by a non-probability consecutive sampling technique contained by ayear i.e., from 1st January 2019 to 31 December 2019 after approval by the Ethical Committee of LUMHS Jamshoro, LUMHS/REC/-752.Informed consent was taken by patients/guardians. Detailed medical history was taken followed by a thorough clinical examination of patients presented with clinical susceptibility to typhoid fever.All diagnosed patients of typhoid fever, either gender,age range from 2-12 years were included and patients with allergy to cefixime or macrolides, for most complications of typhoid fever-like intestinal perforation,septicemia,dysphagia,oral medications and substantial disease underneath, requiring chronic medication and immune-deficiencies were excluded from the study. A sample size of 270 patients (135 in each group) was calculated with an 80% confidence level, 4.66% absolute precision and by taking an expected percentage of the cure rate of Azithromycin and cefixime as 87% (0.87) and 93% (0.93) for treating typhoid fever among children[13]. Diagnosed cases of typhoid fever based on blood culture (before treatment) were enrolled in the study and they were equally divided into two groups (Group-I135 azithromycin recipients and Group-II135 cefiximerecipients).All patients wereadmitted through the Outpatient Department (OPD) or Emergency Room (ER) in the pediatric ward. Reports on patient demographics, present complaints, symptoms, and temperature were recorded. Detailed history, blood count and differential count were sent at baseline for a blood sample, and the study group was randomly divided into two groupings, Azithromycinrecipients received orally100mg/kg/day, OD, and cefixime10 mg/kg/12 hourly. Every day, each patient will be evaluated and proforma updated in terms of appetite, hepatomegaly, splenomegaly, constipation/diarrhea, headache, and abdominal pain. Blood culture was performed on day one and day ten for correlation to treatment effectiveness.SPSS version 26.0 was used for the data analysis. Quantitative data were presented with mean±SD and qualitative data with frequency and percentage. Comparison of qualitative variables between groups was done with the Chi-Square test and the comparison of quantitative variables between groups was done with the help of the Independent sample t-test.p-value <0.05 was considered statistically significant.

RESULTS

Of the total sample,144 (53.3%)of the sample was aged between 2 to 5 years,81(30%) patients were seen in the age group 6 to 9 years and 45 (16.6%) observed in the age group10 to 12 years with the mean age.Gender distribution shows a male predominance in both groups 156 (57.8%) were male and 114(42.2%)were female(Table 1).

Table 1: Demographic Characteristics of Participants

Age (Years)	Group I	Group II
2-5	60 (44.44%)	84 (62.22%)
6-9	47 (34.82%)	34 (25.19%)
10-12	28 (20.74%)	17 (12.59%)
Mean ±SD	8.16±7.815	7.60±8.518
Gender	**Male**	**Female**
Group I	86 (63.70)	49 (36.30)
Group II	70 (51.86)	65 (48.14)

Signs and symptoms observed on admissions of patients between groups.On admission, signs and symptoms were seen among all the patients. The mean + SD of haemoglobin count was noted in Group I (9.200±1.4300) and Group II was (9.457±1.4712) and the Mean + SD of total leukocyte was noted in Group I (31.466±156.4817) and Group II was (17.669±2.2507).Out of 270 patients, fever was present in 266(98.5%) patients and abdominal pain was seen in 252 patients.(93.3%),83 (30.7%) patients had constipation,diarrhea was present in 177 (65.6%) and the headache was present in 144 patients(53.3%)(Table 2).

Table 2: Signs and Symptoms Observed on Admissions of Patients Between Groups

Variable	Group I	Group II	p-Value
Haemoglobin	9.200±1.4300	9.457±1.4712	0.147
TotalLeucocyteCount	31.466±156.4817	17.669±2.2507	0.307
Fever			
Yes	134 (99.3%)	132 (97.8%)	0.62
No	1 (0.7%)	3 (2.2%)	
Abdominal Pain			
Yes	128 (94.8%)	124 (91.9%)	0.46
No	7 (5.2%)	11 (8.1%)	
Constipation			
Yes	33 (24.4)	50 (37%)	0.03
No	102 (75.6%)	85 (63%)	

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Diarrhea			
Yes	89 (65.9%)	88 (65.19)	0.59
No	46 (34.1)	47 (34.81)	
Headache			
Yes	84 (62.2%)	60 (44.4%)	0.005
No	51 (37.8%)	75 (55.6%)	

Microbial elimination occurred significantly in 110(81.4%) of 135 patients cured with azithromycin versus 68(50.3%) of 135 patients treated with cefixime (p-value=0.005).The patient with microbiological failure in the azithromycin group had Salmonella Typhi isolated from blood on both day 05 and day 10, whereas the patient with microbiological failure in the cefixime group had Salmonella Typhi isolated from blood on day 10(table 3).

Table 3: Patients 'Distribution According to Blood Culture after Therapy

Blood culture after therapy	Azithromycin	Cefixime	Total	p-value
Postive	25 (18.6%)	67(49.7%)	92 (34.0%)	0.001
Negative	110 (81.4%)	68 (50.3%)	178 (66.0%)	

The distribution of patients according to efficacy between groups was done. Clinical cure occurred in 110 (81.4%) of 135 patients treated with azithromycin, compared with 68(50.3%) of 135 patients treated with cefixime (p-value=0.005). Of these, 25 patients with clinical failure in the azithromycin group, 67 had failed in the cefixime group as a result of the slow declaration of fever (Table 4).

Table 4: Distribution of Patients According to Efficacy between Groups

Efficacy	Group I	Group II	p-value
Yes	110 (81.4%)	68 (50.3%)	0.005
No	25 (18.6%)	67 (49.7%)	

DISCUSSION

Malaise, fever, pain and discomfort of the abdomen, rose-colored eruptions, splenomegaly, occasionally hepatomegaly, constipation, diarrhea, toxemia, and leukopenia are the main symptoms of typhoid fever. Large-scale occurrences of typhoid disease persist in nations with inadequate sanitation. Since typhoid fever causes a high rate of morbidity and mortality, it has been identified as the most contagious disease in South Asian nations like Pakistan [15]. Several cases are recorded nationwide each year. It predominates in places with a dearth of sanitary food and safe drinking water. Like other Asian nations, typhoid fever is influenced by various socioeconomic factors [16-17]. In Pakistan, typhoid fever is a very common sickness. Third-generation cephalosporin is becoming the drug of choice more often due to multidrug-resistant (MDR) strains in these regions; however, these drug classes have poor cellular penetrance, which results in poor overall clinical outcomes indicators such as prolonged fever clearance time. Alternative medication regimens are also recommended, such as azithromycin monotherapy [18]. According to this study, children with simple typhoid fever can benefit from a 6-day azithromycin therapy. These patients' clinical and microbiological cure rates were close to 80% [19, 20]. The most frequently reported symptoms among the patients in this study were fever (98.5%), followed by diarrhea (65.5%) and abdominal discomfort (93.3%). Our findings concurred with those of Gamal *et al.*, [21]. It has been demonstrated that typhoid is prevalent in Southeast Asian newborns and young children. The majority of research categorized by gender revealed that typhoid affects men more frequently than women. For example, males were more affected than females in an Iraqi study by Medhat and Aljanabay [22]. Male may be more likely to be affected than females since they spend more time outside the home than females, among other possible explanations. The developing children's underdeveloped immune systems are one of the causes of ages 1 to 10 being susceptible, immature immune system in growing children makes them exposed to this enteric pathogen [10]. In this study, Azithromycin was used on a low dose of 6 days once a day and was compared with cefixime. One reason is for this to be reduced in azithromycin-related side effects and this low dose in typhoid fever has already been demonstrated to be effective in studies that have not made a comparison. The positive outcome of this study led us to test if a shorter course of treatment in children could also be used. The current trials end the message that oral azithromycin with a dose of 10 mg/kg/ day, OD, is better for clinical cures for 6 days compared with 100 mg/kg/day in intravenous ceftriaxone at 2 doses divided over seven days. In children with an efficacy rate of more than 95%,azithromycin is apparently an effective drug for treating straightforward typhoid fever. In previous studies with azithromycin treatment, failure rates of 9.3% were observed [11]. A compared, randomized trial conducted by Giri *et al.*, [23] shown that azithromycin is a very successful treatment for children with uncomplicated typhoid fever. Results of the current study showed that participants taking either azithromycin had clinical and microbiological cure rates of 80%, which compares favourable to results from previous trials using conventional antibiotics to treat typhoid fever. Compared to the third-generation cephalosporin, azithromycin is significantly less expensive and appears to be a good substitute. Convenient once-daily azithromycin dosage combined with a brief treatment duration might increase patient compliance. Therefore, the biggest benefit would still be how simple it is to treat typhoid fever.

CONCLUSIONS

It was concluded that in children, oral azithromycin (10mg/kg/day for 6 days) is more effective than cefixime (20mg/kg/day for 10 days) for the therapy of typhoid fever. Clinical cure occurred 81% of the patients treated with azithromycin, compared with 50% of the patients treated

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with cefixime. Every day taking of oral azithromycin may present a plain cure for typhoid fever brought on by drug-resistant or susceptible strains of Salmonella Typhi, which makes it potentially useful in places with limited access to healthcare services. Most of the children aged between 2 to 5 years with male predominance were affected.

Authors Contribution

Conceptualization: RAU, KA
Methodology: RAU, GSS
Formal analysis: RAU
Writing review and editing: SP, MN

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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