Original Research Article

Typhoid Fever: Azithromycin vs. Ceftriaxone for the Treatment of Mild to Moderate Cases in Children

ABSTRACT

Background: Typhoid fever is a bacterial infection that can spread throughout the body, affecting many organs. Without prompt treatment, it can cause serious complications and can be fatal. It's caused by a bacterium called Salmonella typhi, In areas where there are few carriers of the typhoid bacterium, the disease is uncommon. It's also unusual to find places with sanitary water treatment and waste management systems.Nowadays both Azithromycin and Ceftriaxone are used for the treatment of mild to moderate cases in children.

Objective: To assess the outcome of treatment of Acute Typhoid Fever with Azithromycin vs Ceftriaxone in Children with no other complication.

Method: This comparative study was carried out attertiary hospital from January 2019 to January 2020. Where 200 patients coming to the hospital were initially screened in the outpatient department. During the study period, all children 5-18 years of age who, according to the outpatient department physician, had a diagnosis of typhoid fever were admitted to hospital. After admission to the ward, Among 200 patients, 100 patients treated with azithromycin (7 days of 10 mg/kg/day (maximum dose, 500 mg/day) and 100 patients treated with ceftriaxone were cured ($P > .05$).

Results: Sixty percent of the participants in the research reported drinking alcohol, with the majority (60%) being males between the ages of 5 and 10. Eighty percent of patients had developed a taste for just home-cooked meals and takeout before receiving any bottled water. Patients with typhoid fever whose blood culture results were positive were compared to patients treated with ceftriaxone; those treated with azithromycin had a longer hospital stay on average (9.8 days) and a higher rate (100 instances) of salmonella typhi positivity. Whereas in Ceftriaxone group mean duration of hospital stay was 9.0 days followed by 100 cases that showed positivity in salmonella typhi positive. In azithromycin group 90% were cured by day 7 followed by 86% were cured microbiologically, plus no relapse cases were found. Whereas in ceftriaxone case 80% were cured by day 7 followed

by 78% were cured microbiologically, plus 5 relapse cases werefound.

Conclusion: Oral azithromycin administered once daily appears to be effective for the treatment of uncomplicated typhoid fever in children. If these results are confirmed, the agent could be a convenient alternative for the treatment of typhoid fever, especially in individuals in developing countries where medical resources are scarce.

Keywords: Typhoid Fever, Azithromycin, Ceftriaxone

INTRODUCTION

Children in underdeveloped countries, notably those in Asia and Africa, are particularly vulnerable to typhoid fever, a systemic illness caused by Salmonella and Salmonella paratyphi [1]. Chloramphenicol has been used to treat typhoid fever for decades [2, 3] due to its effectiveness against Salmonella typhi and S. paratyphi. The extensive proliferation of drug-resistant S. typhi has, however, prompted the exploration of other treatment approaches [4]. While fluoroquinolones have been shown to be beneficial, their usage is now limited in children because of the emergence of quinolone-resistant strains of Salmonella typhi [5, 6]. With its superior efficacy against S. typhi, the third-generation cephalosporin ceftriaxone has supplanted other treatments as the gold standard for typhoid fever in many countries [7]. Ceftriaxone is a less-than-ideal therapy option due to the need of parenteral administration.

The macrolide family of medicines gives doctors more tools to combat typhoid. The first macrolide to be tested, azithromycin, has been shown to be effective against various intestinal intracellular infections in vitro [8-10]. Azithromycin has been shown to be extremely efficient in animal models against Salmonella enteritidis and Salmonella typhimurium, with medication efficiency correlated with the tissue concentration of the antibiotic rather than the serum concentration of the drug [11, 12]. Human volunteer studies have indicated that the quantity of azithromycin in neutrophils is more than 100 times that seen in serum [13]. Concentrations of azithromycin in neutrophils were >20 times the normal MIC for S. typhi 5 days after a 3-day course of treatment was finished, although quantities of azithromycin in the serum were undetectable [13].

Based on these promising findings, we decided to start a human study of azithromycin therapy. Azithromycin was first shown to be efficacious in treating adults with

uncomplicated typhoid fever in an open-labeled, nonrandomized study [14]. Thereafter, a randomized study showed that azithromycin was just as effective as ciprofloxacin in treating people with uncomplicated typhoid fever [15]. The present study, which compares the effectiveness of azithromycin suspension and ceftriaxone in treating uncomplicated typhoid fever in children and adults, was motivated by these earlier studies.

OBJECTIVE

To assess the outcome of treatment of Acute Typhoid Fever with Azithromycin vs Ceftriaxone in Children with no other complication.

METHODOLOGY

This comparative study was carried out at a tertiary hospital from January 2019 to January 2020. Where 200 patients coming to the hospital were initially screened in the outpatient department. During the study period, all children of 5-18 years of age who, according to the outpatient department physician, had a clinical diagnosis of typhoid fever were admitted to a single ward in the hospital. After admission to the ward, a study physician reevaluated the patients to determine whether they were eligible for enrollment in the study. Among 200 of patients, 100 patients treated with azithromycin 7 days of 10 mg/kg/day (maximum dose, 500 mg/day) and 100 patients treated with ceftriaxone were included in the study ($P > .05$). Eligibility for enrollment required that a subject have a documented fever (temperature,
$\geqslant$38.5°C) and a history of fever for at least 4 days plus at least 2 of the following criteria: abdominal tenderness, hepatomegaly, splenomegaly, and/or rose spots. Subjects with the following conditions were excluded from the study: allergy to ceftriaxone or erythromycin (or to other macrolides), major complications of typhoid fever (e.g., pneumonia, intestinal hemorrhage or perforation, shock, or coma), inability to swallow oral medication, significant underlying illness (e.g., heart disease, asthma requiring chronic medications, or immunodeficiencies), or treatment within the past 4 days with either study medication or chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMZ), or ampicillin. Subjects who might be pregnant due to their early marriage (age 18) or who were lactating were also excluded from the study. Parents of children meeting eligibility requirements were asked to have their child enroll in the study, and if they agreed, informed consent was obtained before randomization of the study drug.

RESULTS

Table-1 shows age distribution of the patients where majority belong to 5-8years age group. followed by 30% belong to 09-11years age group and 20% belong to 12-18 years age group.

Table-1: Age distribution of the patients

Age distribution of the patients	Percentage (%)
5-8 years	50%
9-11 years	30%
12-18 years	20%

Figure-1 shows gender status of the patients where 55% were male and 45% were female.

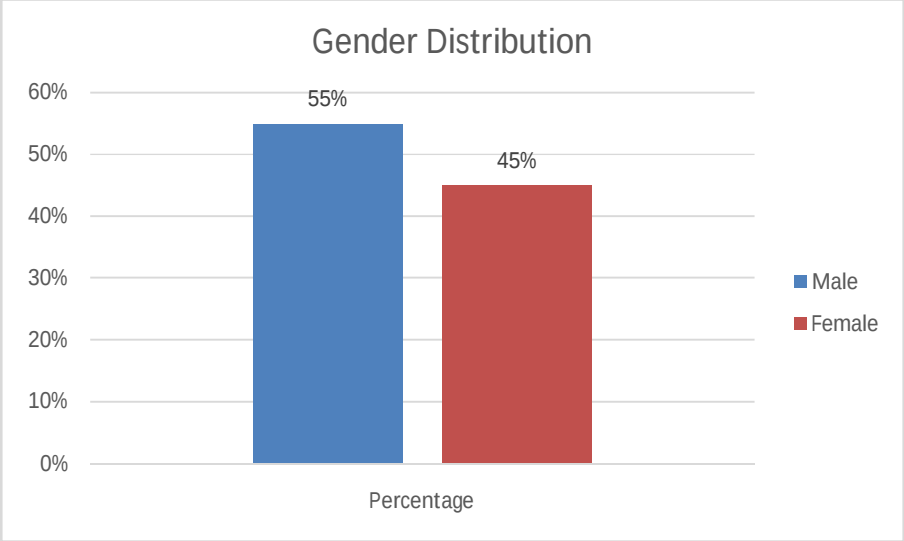

Figure-1: Gender distribution

Table-2 shows demographic status of the patients where 45% live in semipucca building followed by 60% drink Supply water without boiling and 80% cases were accustomed to solely homemade food and outside of food. Moreover, significance association were noticed in food habit and drinking water source of the patients.

Table-2: Demographic status of the patients

Demographic status	Percentage (%)	P value
Housing status:		

Kacca	20%	0.213
Semipucca	45%	
Pucca	35%	
Drinking water source:		0.0001
Tubewell	10%	
Supply water without boiling	60%	
Supply water with boiling	30%	
Food habit: • Accustomed to solely homemade food • Used to eating only homemade and non-prepared foods	20% 80%	0.002

Figure-2 shows Distribution of patients by liver status where 75% had palpable liver status.

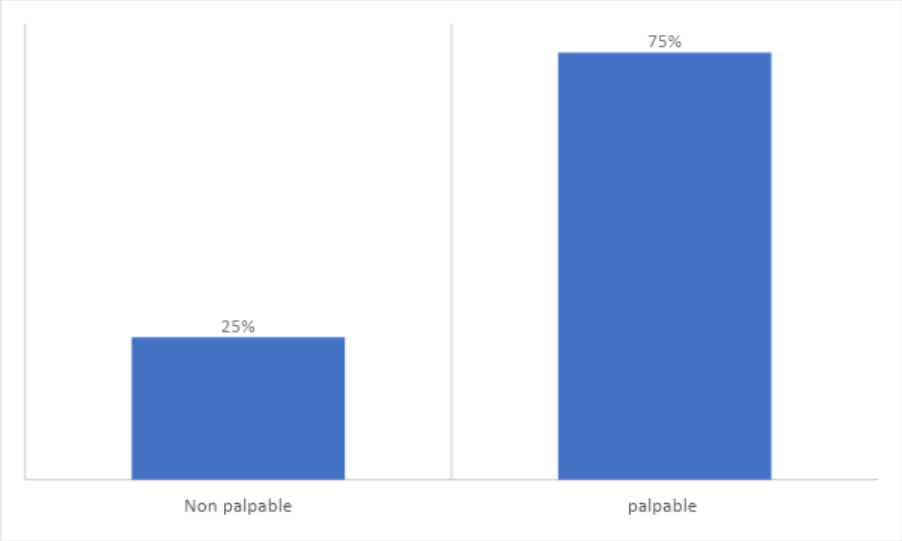

Figure-2: Distribution of patients by liver status x2= 5.486; df=1; P = 0.014

Table-3 shows clinical characteristics of azithromycin and ceftriaxone recipients who had typhoid fever and for whom blood cultures were positive where in azithromycin group mean duration of hospital stay was 9.8 days followed by 100 cases showed positivity in salmonella typhi positive. Whereas in Ceftriaxone group mean duration of hospital stay was 9.0 days followed by 100 cases showed positivity in salmonella typhi positive.

Table-3: Clinical characteristics of azithromycin and ceftriaxone recipients who had typhoid fever and for whom bloodcultures

Clinical characteristics (During admission)	Azithromycin group, n=100	Ceftriaxone group, n=100	P value
Mean Duration of fever before admission, days	**9.8**	**9.0**	**0.234**
Blood culture result • **Salmonella typhi** • **Salmonella paratyphi**	**100**	**100**	**0.121**
Blood culture that yielded MDRS. typhi	**6**	**7**	**0.112**

Table-4 shows laboratory status of the patients during admission where in azithromycin groupmean hemoglobin level was 10.6±1.4 g/dl followed by mean WBC count was 6.0±2.3 cells/mm3, Total bilirubin level 0.3±0.1 mg/dL. Whereas in Ceftriaxone group mean hemoglobin level was 10.9±1.4 g/dl followed by mean WBC count was 6.5±2.3 cells/mm3, Total bilirubin level 0.4±0.1 mg/dL.

Table-4: Laboratory status of the patients during admission

Laboratory characteristics (During admission)	Azithromycin group, n=100	Ceftriaxone group, n=100	P value
Hemoglobin level, g/dL (11–18)	10.6±1.4	10.9±1.2	**0.111**
WBC count, cells/mm3(4.5–10.53 103)	6.0±2.3	6.5±1.6	**0.121**

Platelet count, cells/mm3(150,000–350,000)	213,000±75,000	215,000±96,000	**0.100**
Total bilirubin level, mg/dL (0.2–1.0)	0.3±0.1	0.4±0.1	**0.321**
AST level, U/L (0–33)	89±48	84±70	**0.201**
Blood urea nitrogen level, mg/dL (7–18)	10.5±3.1	11.6±6	**0.111**
Serum creatinine level, mg/dL (0.7–1.5)	0.8±0.1	0.7±0.2	**0.506**

Table-5 shows mean Laboratory test result on day 10 where after 10 days in azithromycin group mean hemoglobin level was 9.8±1.4g/dl followed by mean WBC count was 6.2±1.6cells/mm3, Total platelet count 433,000±122,000 cells/mm3. Whereas in Ceftriaxone group mean hemoglobin level was 10.5±1.0 g/dl followed by mean WBC count was 7.4±2.2cells/mm3, Total platelet count431,000±164,000cells/mm3.

Table-5: Laboratory test result on day 10

Laboratory characteristics, day 10	**Azithromycin group, n=100**	**Ceftriaxone group, n=100**	**P value**
Hemoglobin level, g/dL (11–18)	9.8±1.4	10.5±1.0	**0.111**
WBC count, cells/mm3(4.5–10.53 103)	6.2±1.6	7.4±2.2	**0.120**
Platelet count, cells/mm3(150,000–350,000)	433,000±122,000	431,000±164,000	**0.101**
Total bilirubin level, mg/dL (0.2–1.0)	0.3±0.1	0.4±0.2	**0.321**

AST level, U/L (0–33)	52±29	60±35	**0.0.23**
Blood urea nitrogen level, mg/dL (7–18)	9.0±3.1	9.6±6	**0.111**
Serum creatinine level, mg/dL (0.7–1.5)	0.6±0.1	0.7±0.2	**0.506**

Table-6 shows Responses to treatment with azithromycin or ceftriaxone among patient where in azithromycin group 90% were cured by day 7 followed by 86% were cured microbiologically, plus no relapse cases were found. Whereas in ceftriaxone case 80% were cured by day 7 followed by 78% were cured microbiologically, plus 5 relapse cases werefound.

Table-6: Responses to treatment with azithromycin or ceftriaxone among patient

Response to treatment	**Azithromycin group, n=100**	**Ceftriaxone group, n=100**	**P value**
Clinical cure by day 7	45 (90%)	40(80%)	0.001
Duration of fever after starting therapy, meand±SD	4.0±1.1	3.7±1.1	0.212
Microbiological cure, no. (%)	43 (86%)	39(78%)	0.121
Blood culture that yielded Salmonellaon **Day 4** **Day 10**	 1a 1a	 0 1	0.001
Stool culture that yielded Salmonella on day 10	0	0	0.0001

Relapse	0	5	

DISCUSSION

We found that azithromycin is very successful in treating children with uncomplicated typhoid fever in a randomized, controlled study. Results from this research are comparable to those from previous studies of conventional antibiotics for the treatment of typhoid fever [2, 6, 19-21], with clinical cure rates of >90% and microbiological cure rates of >95% for participants taking either azithromycin or ceftriaxone. Relapses of infection occurred in 14% of ceftriaxone-treated participants with bacteremia within 1 month after medication completion, which is an intriguing finding. These findings are in line with the 5-15% recurrence rate seen in earlier ceftriaxone for typhoid fever studies [2, 7, 19, 22]. The lengthy half-life of azithromycin inside the intracellular compartment, with elimination of remaining organisms after conclusion of treatment, and its higher concentration within the biliary system may account for the lack of relapses in our small sample of azithromycin-treated subjects. Because of its extraordinarily long half-life in tissue, azithromycin may be amenable to shorter durations of therapy for typhoid fever, similar to those that have been attempted with effectiveness for quinolone antibiotics [6, 19, 23].

Other study found that, the patients treated with ciprofloxacin showed a slightly shorter mean time to defervescence (3.3 days) than did patients treated with azithromycin (3.8 days), but this difference was not statistically significant ($P > 0.05$). Stool cultures of all patients were negative during and after therapy, and no relapses were detected after therapy. Adverse events of nausea or vomiting, lightheadedness, dry throat or mouth, and loose stools were reported occasionally in both groups. These events were mild or moderate and did not result in interruption of therapy and could be attributed in part to the enteric infections. Laboratory results showed that rises in AST values occurred in some patients after therapy, with the mean AST being higher in the group treated with ciprofloxacin than in the group treated with azithromycin; however, the difference between the mean values was not statistically significant ($P > 0.05$), and these results could have been caused, in part, by typhoid fever. [24]

Which is supported to our study where we also found not much of a clinical difference between the two groups. Defervescence occurred significantly sooner in ceftriaxone-treated patients (3.9 days) compared to azithromycin-treated patients (4.1 days), but this

difference was not statistically significant, and both outcomes were within the ranges described in prior typhoid therapy studies [3, 19, 23–25]. Both groups had mild, short-lived gastrointestinal problems, but none were considered serious enough to warranta treatment change.

CONCLUSION

In conclusion, 7 days of 10 mg/kg/day (maximum dose, 500 mg/day) azithromycin seems to be extremely successful for the treatment of uncomplicated typhoid fever in children, with clinical cure rates equivalent to those for ceftriaxone. Typhoid fever caused by susceptible ordrug-resistant strains of S.typhi may be treatable with a straightforward, once-daily oral regimen of azithromycin, making it an appealing option for usage in resource-poor settings.

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