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ORIGINAL ARTICLE

Comparison of efficacy of intravenous ceftraixone versus oral azithromycin in uncomplicated enteric fever.

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ABSTRACT… Objective: To compare the efficacy of intravenous ceftriaxone vs oral azithromycin in uncomplicated enteric fever. **Study Design:** Prospective Cohort study. **Setting:** Department of Pediatric, The National Institute of Child Health Karachi, **Period:** 23 January 2024 to 22 July 2024. **Methods:** 160 patients presented with uncomplicated enteric fever were distributed randomly in ceftriaxone and azithromycin group. Children in the ceftriaxone group received the dose of 75 mg/kg/day intravenously in 2 divided doses, while children in the azithromycin group received the dose of 20 mg/kg/day as a single oral dose for 7 days. Clinical and microbiological efficacy were confirmed on resolution of all symptoms and negative blood culture for Salmonella typhi, respectively. **Results:** Clinical cure was significantly (p-value = 0.027) higher with oral azithromycin than with intravenous ceftriaxone [77 (96.3%) vs. 68 (85.0%)]. Microbiological cure was significantly (p-value = 0.028) higher with oral azithromycin than with intravenous ceftriaxone [80 (100.0%) vs. 74 (92.5%)]. The mean duration to become afebrile after initiating treatment was also significantly ($p<0.001$) shorter with oral azithromycin than with intravenous ceftriaxone [3.98 ± 0.80 days vs. 5.40 ± 1.62 days]. **Conclusion:** Oral azithromycin is more effective than intravenous ceftriaxone in the management of uncomplicated enteric fever with respect to clinical cure, microbiological cure and duration to become afebrile.

Key words: Disease, Enteric Fever, Health, Mortality, Pediatric.

INTRODUCTION

Enteric fever, also known as typhoid fever, is a potentially fatal community-acquired multisystemic illness that remains a public health problem in developing as well as developed countries. It is significantly associated with morbidity and mortality in resource-limited, overcrowded communities with poor health care facilities and access to sanitation. The rate of enteric fever infection is higher in children, which reflects the active transmission in a community.[1,2] Enteric fever prevalence is high among poor countries due to fecally contaminated water and food.[3] In 2017, the global burden of enteric fever was estimated at approximately 14.3 million and 135.9 thousand deaths. Most deaths occurred in children, the elderly, and people living in developing countries.[4]

Salmonella typhi (S. Typhi), a gram-negative bacterium, is the most common cause of enteric fever, while Salmonella paratyphoid A, B, and C are less frequent causes.[5] These microbes are human host-restricted pathogens that are spread through food and water contaminated with feces.[6,7] According to the Global Health Data Exchange, approximately 5,640,277.05 incidences and 71,201.15 deaths were reported globally due to enteric fever in 2021 in children aged 0–14 years. Of these, approximately 4,084,361.28 cases and 47,302.54 deaths occurred in South Asia, of which 489,155.23 cases and 8,446.70 deaths occurred in Pakistan.[8]

Antibiotic resistance is a major problem in the treatment of enteric fever. The development of multidrug resistance (MDR) against S. typhi has limited treatment options, particularly in South Asian countries, including Pakistan.[9,10] In Pakistan, MDR and extensively drug-resistant

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(XDR) strains of S. typhi are increasing day by day and are considered a major public health problem. About 16% and 54% of S. typhi isolates have been reported to be resistant to first-line and second-line antibiotics, respectively.[11,12]

Ceftriaxone and other third-generation cephalosporins are the drug of choice and effective in the treatment of enteric fever, but they are associated with high cost and the requirement of parenteral administration that enforce the use of other effective oral therapies, such as azithromycin, an effective and convenient antibiotic for the treatment of enteric fever.[13-16] A Pakistani study by Khokar et al., reported 88.9% efficacy with ceftriaxone and 93.3% efficacy with azithromycin.[13] Another Pakistani study by Saeed et al., reported 86% efficacy with ceftriaxone and 80% efficacy with azithromycin.[14] Sreenivasa et al., reported 86% and 98% clinical efficacy and 98% and 100 microbiological efficacy with ceftriaxone and azithromycin, respectively.[15]

The study is designed to compare the efficacy of intravenous ceftriaxone and oral azithromycin in children presented with uncomplicated enteric fever in the National Institute of Child Health Karachi. Results will be helpful in the selection of an appropriate and more effective drug in the treatment of uncomplicated enteric fever in children that will reduce the complications and mortality associated with uncomplicated enteric fever. It will also be helpful in decreasing the risk of infections, complications, and child discomfort associated with intravenous therapy. Selection of azithromycin will also decrease the therapy expenditure and decrease the hospital stay.

METHODS

A prospective cohort was carried out on inpatients and outpatients visiting or admitted to the pediatric department of the National Institute of Child Health Karachi. During the period of six months from 23 January 2024 to 22 July 2024, children presented with uncomplicated enteric fever were enrolled by using the consecutive sampling technique. The study includes (1) children of either gender, (2) children with an age of 2 to 14 years, and (3) diagnosed cases of uncomplicated enteric fever. The study excludes (1) children with complicated enteric fever, (2) children of known allergies to ceftriaxone or azithromycin, (3) children who are resistant to ceftriaxone or azithromycin, (4) children who received the antibiotic treatment against S. typhi within the past 4 days, and parents of children not ready to be a part of the study.

Uncomplicated enteric fever was confirmed in children who were presented with fever (temperature ≥ 38.5 °C of at least 4 days) along with two or more than two of the following symptoms, including toxic physical appearance (such as pallor, lethargy, or irritability), tachypnea, coated tongue, abdominal pain, hepatomegaly, and splenomegaly, and the diagnosis was confirmed with a positive blood culture for Salmonella typhi (S. typhi). Clinical effectiveness of ceftriaxone and azithromycin was confirmed when all symptoms resolved after seven days of treatment, while microbiological effectiveness was confirmed with a negative blood culture for Salmonella Typhi (S. Typhi) on day 10.

Online Open Epi Sample size software for calculating two groups sample size was used with proportion of Sreenivasa et al., who reported the 86% clinical efficacy with ceftriaxone and 98% clinical efficacy with azithromycin15, by taking confidential interval 95%, power 80%, and ratio of sample size 1. Sample size was calculated at n = 160 (80 in each group). In Group A (intravenous ceftriaxone group), 80 patients were diagnosed with uncomplicated enteric fever and treated with intravenous ceftriaxone, while in Group B (oral azithromycin group), 80 patients were diagnosed with uncomplicated enteric fever and treated with oral azithromycin.

Study permission was obtained from the institutional ethical review board of the National Institute of Child Health Karachi (letter number: IERB-52/2022, Dated: 23-01-2024), and written informed consent was obtained from the caregivers of children. Children fulfilling the inclusion and exclusion criteria of the study were selected in the study. Demographic details of each child were obtained either from parents or

from medical records, including the name and age of the child. Disease details of each child were enquired, such as duration of symptoms and signs and symptoms, followed by clinical examination for confirmation of hepatomegaly and splenomegaly. A complete blood count and blood culture of each child was performed. Children with uncomplicated enteric fever were distributed randomly in both groups, i.e., the ceftriaxone group and the azithromycin group. Children with resistance to IV ceftriaxone were treated with oral azithromycin, while children without resistance were treated with IV ceftriaxone. Children in the ceftriaxone group received the dose of 75 mg/kg/day intravenously in two equally divided doses for 7 days, while children in the azithromycin group received the dose of 20 mg/kg/day as a single oral dose for 7 days. At the end of therapy (after 7 days), each child was clinically evaluated for obtaining clinical efficacy of both drugs, while after 10 days of therapy, a blood culture was performed for obtaining microbiological efficacy of both drugs. All the data will be recorded in proforma by the researcher. Statistical Package for Social Science (SPSS) software, Version 25, was used for interpretation of collected data. Mean and standard deviation were calculated for quantitative variables and frequency tables for qualitative variables. Effect modifiers such as gender and age in groups and duration of disease were controlled by stratification in both groups. A post-stratification chi-square test was applied by taking a p value ≤ 0.05 as significant.

RESULTS

Of the 160 children, 43 (53.8%) and 42 (52.5%) were male, and 37 (46.3%) and 38 (47.5%) were female, in groups A (intravenous ceftriaxone) and B (oral azithromycin), respectively. The mean age was 6.79 ± 3.37 years and 6.88 ± 3.49 years in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. The majority of children, 45 (56.3%) and 43 (53.8%) were ≤ 5 years of age in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. There was no significant difference in the demographics of both groups (Table-I).

Fever was the most common clinical presentation of uncomplicated enteric fever reported in all children of both groups. The mean duration of fever was 8.78 ± 3.16 days and 8.79 ± 3.40 days in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. The other commonly observed symptoms of uncomplicated enteric fever were pallor 25 (31.3%) and 28 (35.0%), lethargic 28 (35.0%) and 30 (37.5%), tachypnea 18 (22.5%) and 16 (20.0%), abdominal pain 22 (27.5%) and 19 (23.8%), coated tongue 13 (16.3%) and 15 (18.8%), hepatomegaly 35 (43.8%) and 34 (42.5%), and splenomegaly 7 (8.8%) and 6 (7.5%) in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. There was no significant difference in the clinical presentation of both groups (Table-I).

Clinical cure was significantly (p-value = 0.027) higher with oral azithromycin than with intravenous ceftriaxone [77 (96.3%) vs. 68 (85.0%)]. Similarly, microbiological cure was significantly (p-value = 0.028) higher with oral azithromycin than with intravenous ceftriaxone [80 (100.0%) vs. 74 (92.5%)]. The mean duration to become afebrile after initiating treatment was also significantly (p-value <0.001) shorter with oral azithromycin than with intravenous ceftriaxone [3.98 ± 0.80 days vs. 5.40 ± 1.62 days]. There was no significant difference in the adverse effects of both groups (Table-II).

DISCUSSION

Enteric fever is a serious medical condition in developing countries like Pakistan, but it is rapidly becoming a global health problem due to the rise of resistant strains of Salmonella typhi and paratyphi.[17,18] Most first-line drugs, such as quinolones and cephalosporins, have demonstrated resistance.[19-21] Only a few studies have shown that azithromycin is effective in adults and children with uncomplicated enteric fever.[13-16,22]

This study enrolled 160 consecutive children with uncomplicated enteric fever and evaluated the efficacy of intravenous ceftriaxone and oral azithromycin in the treatment of uncomplicated enteric fever.

Variables		Group A (n=80)	Group B (n=80)	P-Value
Demographics				
Gender	Male	43 (53.8%)	42 (52.5%)	0.874
	Female	37 (46.3%)	38 (47.5%)	
Age (Years)	Mean ± SD	6.79 ± 3.37	6.88 ± 3.49	0.881
	≤5	45 (56.3%)	43 (53.8%)	0.938
	6-10	23 (28.7%)	25 (31.3%)	
	11-15	12 (15.0%)	12 (15.0%)	
Clinical Presentation				
Fever	Yes	80 (100.0%)	80 (100.0%)	---
	No	0 (0.0%)	0 (0.0%)	
Duration of Fever	Mean ± SD	8.78 ± 3.16	8.79 ± 3.40	0.981
Pallor	Yes	25 (31.3%)	28 (35.0%)	0.614
	No	55 (68.8%)	52 (65.0%)	
Lethargy	Yes	28 (35.0%)	30 (37.5%)	0.742
	No	52 (65.0%)	50 (62.5%)	
Tachypnea	Yes	18 (22.5%)	16 (20.0%)	0.699
	No	62 (77.5%)	64 (80.0%)	
Abdominal Pain	Yes	22 (27.5%)	19 (23.8%)	0.587
	No	58 (72.5%)	61 (76.3%)	
Coated Tongue	Yes	13 (16.3%)	15 (18.8%)	0.677
	No	67 (83.8%)	65 (81.3%)	
Hepatomegaly	Yes	35 (43.8%)	34 (42.5%)	0.873
	No	45 (56.3%)	46 (57.5%)	
Splenomegaly	Yes	7 (8.8%)	6 (7.5%)	0.772
	No	73 (91.3%)	74 (92.5%)	

Group A: Intravenous Ceftriaxone Group; Group B: Oral Azithromycin Group.

Table-I. Demographics and clinical presentation of children presented with uncomplicated enteric fever

In this study, most of the children 43 (53.8%) and 42 (52.5%) were male, and the remaining 37 (46.3%) and 38 (47.5%) children were female, with an average age of 6.79 ± 3.37 years and 6.88 ± 3.49 years in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. Similar results have been reported by various other researchers, such as Khokar et al., who reported 52.2% male children and 47.8% female children with a mean age of 6.97 ± 3.01 years in both groups (intravenous ceftriaxone and oral azithromycin).[13] Saeed et al. reported 54.0% male children and 46.0% female children with a mean age of 6.68 ± 2.77 and 7.47 ± 2.93 years in the intravenous ceftriaxone and oral azithromycin groups, respectively.[14] Sreenivasa et al. reported a 1.3:1 and 1.02:1 male-to-female ratio with a mean age of 7.3 ± 2.8 and 8.5 ± 3.4 years in the intravenous ceftriaxone and oral azithromycin groups, respectively.[15] Rafique et al. reported 61.8% male children and 38.2% female children with a mean age of 7.35 ± 3.02 and 7.16 ± 3.04 years in the intravenous ceftriaxone and oral azithromycin groups, respectively.[23] In contrast, Nair et al. reported 41.2% and 46.7% male children and 58.8% and 53.3% female children with a mean age of 10.4 ± 3.4 and 11.4 ± 3.6 years in the intravenous ceftriaxone and oral azithromycin groups, respectively.[16] Most studies reported that male children were more likely to have uncomplicated enteric fever.

Variables		Group A (n=80)	Group B (n=80)	P-Value
Clinical Cure	Yes	68 (85.0%)	77 (96.3%)	0.027
	No	12 (15.0%)	3 (3.8%)	
Microbiological Cure	Yes	74 (92.5%)	80 (100.0%)	0.028
	No	6 (7.5%)	0 (0.0%)	
Duration to become Afebrile (Days)	Mean ± SD	5.40 ± 1.62	3.98 ± 0.80	<0.001
Adverse Effects				
Nausea	Yes	14 (17.5%)	17 (21.3%)	0.548
	No	66 (82.5%)	63 (78.8%)	
Vomiting	Yes	17 (21.3%)	18 (22.5%)	0.848
	No	63 (78.8%)	62 (77.5%)	
Diarrhea	Yes	29 (36.3%)	22 (27.5%)	0.235
	No	51 (63.7%)	58 (72.5%)	
Thrombocytopenia	Yes	6 (7.5%)	0 (0.0%)	0.028
	No	74 (92.5%)	80 (100.0%)	

Group A: Intravenous Ceftriaxone Group; Group B: Oral Azithromycin Group.

Table-II. Efficacy of intravenous ceftriaxone & oral azithromycin in children presented with uncomplicated enteric fever

In this study, fever was the most common clinical presentation of uncomplicated enteric fever reported in all children of both groups. The second most common clinical presentation of uncomplicated enteric fever was hepatomegaly observed in 35 (43.8%) and 34 (42.5%) children, followed by lethargy in 28 (35.0%) and 30 (37.5%) children, pallor in 25 (31.3%) and 28 (35.0%) children, abdominal pain in 22 (27.5%) and 19 (23.8%) children, tachypnea in 18 (22.5%) and 16 (20.0%) children, coated tongue in 13 (16.3%) and 15 (18.8%) children, and splenomegaly in 7 (8.8%) and 6 (7.5%) children in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. Similar clinical findings were reported by Nair et al., who also found a higher frequency of hepatomegaly in 29.4% and 46.7% of children presented with uncomplicated enteric fever.[16] Fever was the most common clinical presentation of uncomplicated enteric fever reported by all similar studies.[13-16]

Blood cultures were collected before the first dose of antibiotics on the first day of hospital admission and repeated at day 10 of treatment, regardless of clinical outcome. Both antibiotics (intravenous ceftriaxone and oral azithromycin) were highly effective in the management of uncomplicated enteric fever. In this study, clinical cure was significantly (p-value = 0.027) higher with oral azithromycin than with intravenous ceftriaxone [77 (96.3%) vs. 68 (85.0%)]. Similarly, microbiological cure was significantly (p-value = 0.028) higher with oral azithromycin than with intravenous ceftriaxone [80 (100.0%) vs. 74 (92.5%)]. The mean duration to become afebrile after initiating treatment was also significantly (p-value <0.001) shorter with oral azithromycin than with intravenous ceftriaxone [3.98 ± 0.80 days vs. 5.40 ± 1.62 days]. Similar results have been reported by various other researchers, such as Khokar et al., who reported 88.9% clinical cure with ceftriaxone and 93.3% clinical cure with azithromycin.[13] Saeed et al. reported 86% microbiological cure with ceftriaxone and 80% microbiological cure with azithromycin.[14] Sreenivasa et al. reported 86% clinical cure with ceftriaxone and 98% clinical cure with azithromycin. Similarly, 98% microbiological cure with ceftriaxone and 100% microbiological cure with azithromycin.[15] Nair et al. reported 88.2% clinical cure with ceftriaxone and 100% clinical cure with azithromycin. Similarly, 97% microbiological cure with ceftriaxone and 100%

microbiological cure with azithromycin.[16] Nagaraj et al. reported 93.7% clinical cure with ceftriaxone and 95.2% clinical cure with azithromycin.[24] Rao et al. reported 94% clinical cure with ceftriaxone and 96% clinical cure with azithromycin. Similarly, 96% microbiological cure with ceftriaxone and 98% microbiological cure with azithromycin.[24] All similar studies are reporting that oral azithromycin is more effective than intravenous ceftriaxone in the management of uncomplicated enteric fever.

There was no significant difference in adverse effects between the two treatment groups except for thrombocytopenia, which was only associated with the intravenous ceftriaxone group. Gastrointestinal problems were among the most common minor adverse effects in both treatment groups. Diarrhea was the most common adverse effect reported in 29 (36.3%) and 22 (27.5%) children, followed by vomiting in 17 (21.3%) and 18 (22.5%) children, nausea in 14 (17.5%) and 17 (21.3%) children, and thrombocytopenia in 6 (7.5%) and 0 (0.0%) children in group A (intravenous ceftriaxone) and group B (oral azithromycin), respectively. Similar, minor gastrointestinal side effects were reported by other researchers that were not significantly different between the two treatment groups.[15,16,25]

There was a significant difference between the treatment groups in terms of clinical cure and microbiological cure. Oral azithromycin is more effective than intravenous ceftriaxone in the management of uncomplicated enteric fever. The small sample size and short follow-up of 10 days were major limitations of this study. Further large-scale studies are needed to confirm that azithromycin will not cause the development of resistance and relapse. Vomiting as a minor side effect of oral azithromycin may limit its use in the management of uncomplicated enteric fever.

CONCLUSION

Oral azithromycin is more effective than intravenous ceftriaxone in the management of uncomplicated enteric fever with respect to clinical cure, microbiological cure and duration to become afebrile.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Asma Majeed:** Conceptualized the study, designed study protocols.
2	**Muahmmad Ashfaque:** Designed study protocols, critically reviewed.
3	**Wajid Hussain:** Performed literature search.
4	**Faiqa Hassan:** Data collection, data analysis.
5	**Zara Shoukat:** Data collection.
6	**Mariam Aijaz:** Results writing.