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Research Article

**COMPARISON OF THE CLINICAL EFFECTIVENESS OF
AZITHROMYCIN VERSUS CEFTRIAXONE IN TREATMENT
OF ENTERIC FEVER**¹Muhammad Rafiq Khan, ²Jalil Khan, ³Hamid ullah, ³Muhammad Ali,¹Senior Registrar, Pediatric Medicine Unit, Khalifa Gul Nawaz Teaching Hospital Bannu²Medical Officer, Pediatric Medicine Unit, Khalifa Gul Nawaz Teaching hospital Bannu.³Junior Registrar, Pediatric Medicine Unit, Khalifa Gul Nawaz Teaching Hospital Bannu³Senior Registrar, Pediatric Medicine Unit Mufti Mehmood teaching hospital, D.I.khan**Abstract:**

Introduction: Typhoid fever, an enteric bacterial infection caused by *Salmonella Typhi* and *Salmonella Paratyphi*; is a common and sometimes fatal infection caused in developing countries especially in south Asia because of poor sanitation and unclean water. Chloramphenicol, Ampicillin, Sulfamethoxazole– Trimethoprim and Tetracycline have been traditionally used in the therapy of Typhoid fever.

Objective: To compare Azithromycin versus Ceftriaxone in terms of mean time taken (in number of days) for defervescence in children with enteric fever.

Study design: Randomized controlled trial

Site and duration of study: This study was conducted in the in the Department of Pediatrics Medicine, Khalifa Gul Nawaz, Bannu from 20/03/2018 to 30/06/2018.

Methodology: A total of 140 patients of enteric fever were observed, which were divided in two equal groups.

Hypothesis: Azithromycin is better than Ceftriaxone in term of mean number of days for defervescence.

Sampling technique: Non probability consecutive sampling.

Results: Overall Male to female ratio was 1.61:1. Sex distribution among the groups was insignificant with p -value=0.366. The overall age of the patients was 5.47 years +2.38SD. Defervescence wise distribution shows that Group A have average defervescence of 4.39days + 1.12SD while in Group B it was 4.46 days+1.1017SD which was insignificant with p -value = 0.693.

Conclusion: Mean defervescence time of azithromycin is better than ceftriaxone in the treatment of enteric fever

Key words: Enteric fever, Azithromycin, Ceftriaxone, defervescence.

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INTRODUCTION:

Typhoid fever, an enteric bacterial infection caused by *Salmonella Typhi* and *Salmonella Paratyphi*; is a common and sometimes fatal infection caused in developing countries especially in south Asia because of poor sanitation and unclean water. It is transmitted by fecal oral route and world's estimated more than 22 million cases with 200,000 deaths every year [1]. Chloramphenicol, Ampicillin, Sulfamethoxazole-Trimethoprim and Tetracycline have been traditionally used in the therapy of Typhoid fever. After the resistance of chloramphenicol in 1970s, Quinolones were started as 1st line treatment of typhoid fever in 1990s [2]. Due to the extensive usage of Quinolones, their susceptibility has decreased causing certain strains becoming resistant to them [3]. Ceftriaxone; a third generation cephalosporin, is a highly effective drug and among the most commonly drug used for the treatment of uncomplicated and multi drug resistant typhoid fever [4]. Because of parenteral route of administration and prolonged defervescence time; Ceftriaxone is less than ideal treatment alternative to Quinolones. Moreover resistance is also developing to these Cephalosporins [5]. Azithromycin; first tested in 1990s with good results is very promising alternative to Quinolones and Cephalosporins with good cure rates, oral route of administration and prevention of fecal carriage and relapse [6]. It also has reduced clinical failure, duration of hospital stay and also well tolerated orally as compared to others [7]. Clinical response was studied in one study where Mean time to defervescence was 4.5 ± 1.9 days for patients who received Azithromycin and $3.6 \pm$ for patients who received Ceftriaxone. Clinical cure by day 7 was 94% in patients who received Azithromycin and 97% who received Ceftriaxone [8]. Cost and compliance, as well as safety and efficacy, need to be considered when choosing regimens for treating enteric fever in countries with limited resources where the disease is endemic. Furthermore, there is no local data of Azithromycin efficacy versus Ceftriaxone, and Ceftriaxone is still used as 1st line in outdoor patients. We wanted to compare both the drugs so that better one could be recommended in future.

OBJECTIVE:

To compare Azithromycin versus Ceftriaxone in terms of mean time taken (in number of days) for defervescence in children with enteric fever.

METHODOLOGY:

HYPOTHESIS: Azithromycin is better than Ceftriaxone in term of mean number of days for defervescence.

Study design: Randomized controlled trial.

Site and duration of study: This study was conducted in the in the Department of Pediatrics Medicine, Khalifa Gul Nawaz, Bannu from 20/03/2018 to 30/06/2018.

SAMPLE SELECTION:

Sample size: With the help of WHO Sample Size Calculator, following are the Calculation: Level of Significance 5%, Power of test 80%, Pooled Standard Deviation 1.75, Test value of the population Mean 4.5 [8] , Anticipated population Mean 3.6^8 [8], Sample size = $n =$ Approximately 70 patients in each group.

Sampling technique: Non probability consecutive sampling.

Inclusion Criteria:

- 1.Age: 2-12 years of either sex.
- 2.All children presenting with enteric fever.

Exclusion Criteria:

- 1.Allergic to ceftriaxone or azithromycin.
- 2.Major complications of enteric fever (e.g., pneumonia (CXR), intestinal hemorrhage (stool occult blood) or perforation (Erect Abdomen X-ray), shock, or coma).
- 3.Inability to swallow oral medication.
- 4.Patients with heart disease, asthma requiring chronic medications, or immunodeficiencies (diagnosed on history).
- 5.Treatment within the past 48 hours with study medication or chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMZ), or ampicillin.

OPERATIONAL DEFINITIONS:

Enteric fever: Patients with high grade fever more than 101.6°f ($\geq 38.6^{\circ}\text{C}$) of more than 3 days with patient's Typhidot showing IgM positive.

Mean Defervescence time: The time starting from initiation of therapy, the patient took to become afebrile for a period of 24 hours in term of mean number of days.

DATA COLLECTION PROCEDURE:

The study has approved from hospital ethical committee. Eligible patients were enrolled in trial after taking informed consent. All patients fulfilling the inclusion criteria were included in the study and were admitted in the Inpatient department. Hundred and forty patients were divided into Group A and Group B by lottery method. All patients in Group A were treated with oral azithromycin

suspension/capsule (10mg/kg/day; maximum dose, 500mg/day) were administered once daily for 7 days and Group B with Intravenous (I/V) ceftriaxone (75mg/kg/day; maximum dose, 2.5 g/day) were administered twice daily for 10 days. All medications were administered in the hospital by the nursing staff. The Clinical response to the therapy of both drugs were calculated in terms of number of days taken for defervescence. However if patient was not improved with above medicines, he was managed with suitable alternate medicines till his/her complete recovery, the drug was labeled non effective and the patient were excluded from the study. Data were recorded in predesigned Performa by researcher.

DATA ANALYSIS:

Data were entered and analyzed in SPSS version 10.0. Frequency and percentages were calculated for qualitative variables like gender of patients. Mean and standard deviation was calculated for quantitative variables like age, time of defervescence (days). Independent samples t-test was used to compare time of defervescence (days) in both the groups. $P < 0.05$ was taken as level of significance.

RESULTS:

A total of 140 patients of 2-12 years of age of either gender with enteric fever were observed, which were divided in two equal groups. Patients in Group A were treated with oral azithromycin suspension/capsule (10mg/kg/day; maximum dose, 500mg/day) were administered once daily for 7 days and Group B with Intravenous (I/V) ceftriaxone (75mg/kg/day; maximum dose, 2.5 g/day) were administered twice daily for 10 days.

There were 39(55.7%) male and 31(44.3%) female patients in Group A while 42(60%) were male and 28(40%) were female belonging to Group B. Which was statistically insignificant in both the group with p-value 0.366. Overall male to female ratio is 1.61:1 [Table 1].

Average age was 5.51 years+ 2.42SD in Group A and contains 25(35.5%) patients having less than or equal to 4 years, 30(42.9%) patients 5-7 years, 11(15.7%) patients 8-10 years and 4(5.7%) patients' lies between the age of more than 11 years of age. While group B have average age of 5.42 years +2.35SD and contains 25(35.7%) patients in less than or equal to 4 years, 29(41.4%) in 5-7 years, 14(20%) in 8-10 years and 2(2.9%) patients have age more than 10 years of age. The overall average of the patients was 5.47 years +2.38SD. The age distribution among the group was insignificant with p-value 0.791 [Table 2].

Defervescence wise distribution shows that Group A have average defervescence of 4.39days + 1.12SD while in Group B it was 4.46 days+1.1017SD which was insignificant with p-value = 0.693. Similarly weight is also insignificant in both the groups with p-value=0.823 [Table 3].

When defervescence was stratified among the age over both the group it was shown that age group were insignificant defervescence in both the groups [Table 4].

Similarly when defervescence of the patients were stratified among gender it shows that gender has also insignificant effect in both the groups [Table 5].

TABLE NO: 1: GENDER DISTRIBUTION IN BOTH THE GROUPS

		Groups		Total	p-value
		Group A	Group B		
Gender	Male	39 55.7%	42 60.0%	81 57.9%	0.366
	Female	31 44.3%	28 40.0%	59 42.1%	
Total		70 100.0%	70 100.0%	140 100.0%	

TABLE NO: 2: AGE WISE DISTRIBUTION IN BOTH THE GROUPS

		Groups		Total	p-value
		Group A	Group B		
Age (in years)	<= 4.00	25 35.7%	25 35.7%	50 35.7%	
	5.00 - 7.00	30 42.9%	29 41.4%	59 42.1%	
	8.00 - 10.00	11 15.7%	14 20.0%	25 17.9%	
	11.00+	4 5.7%	2 2.9%	6 4.3%	
Total		70 100.0%	70 100.0%	140 100.0%	
Mean(in years)+SD		5.51 + 2.42	5.42 + 2.35	5.47 + 2.38	

TABLE NO: 3: COMPARISON OF DEFERVESENCE AND WEIGHT IN BOTH THE GROUPS

		Groups	N	Mean	Std. Deviation	p-value
Defervesence (in days)	Group A		70	4.3857	1.12021	0.693
	Group B		70	4.4571	1.01704	
Weight(in Kg)	Group A		70	15.4857	6.91091	0.823
	Group B		70	15.2286	6.64890	

TABLE NO: 4:AGE WISE DISTRIBUTION OF DEFERVESENCE IN BOTH THE GROUPS

		Groups						p-value
		Group A			Group B			
		Defervevence (in days)			Defervevence (in days)			
		Count	Mean	SD	Count	Mean	SD	
Age (year)	(in <= 4.00	25	4.40	1.15	25	4.28	1.10	0.5743
	5.00 - 7.00	30	4.37	1.22	29	4.66	.97	0.3175
	8.00 - 10.00	11	4.45	.93	14	4.43	.94	0.9581
	11.00+	4	4.25	.96	2	4.00	1.41	0.8042

TABLE NO: 5: GENDER WISE DISTRIBUTION OF DEFERVESENCE IN BOTH THE GROUPS

		Groups					p-value	
		Group A			Group B			
		Defervevence(in days)			Defervevence(in days)			
		Count	Mean	SD	Count	Mean		SD
Gender	Male	39	4.46	1.07	42	4.40	1.11	0.8053
	Female	31	4.29	1.19	28	4.54	.88	0.3670

DISCUSSION:

Enteric fever is a potentially fatal multisystem illness caused by *Salmonella typhi* or *Salmonella Paratyphi* [9]. It occurs worldwide where water supply and sanitation are substandard [10]. Enteric fever is highly endemic in developing countries, especially in Asia and Africa, with documented high prevalence among children. It is estimated that more than 26.9 million enteric fever cases occur annually, of which 1% results in death [11, 12].

Azithromycin was tested in the 1990s, with good results, and can now be regarded as a promising alternative to fluoroquinolones and cephalosporins [13-15]. Nine prospective clinical trials employing azithromycin that enrolled culture-positive children and adults with typhoid fever were carried out in Egypt, India, Vietnam, and Bangladesh [16-18]. The drug was received by a total of 453 patients, of whom 268 (59%) were children. Its dosage was 10 or 20 mg/kg/day for children and 500 mg/day or 1 g/day for adults, given orally for 7 days in seven trials and for 5 days in two trials. Two trials were not comparative [14, 19], whereas randomized assignments were made to different comparator drugs in the remaining trials: chloramphenicol in one [15], ciprofloxacin in one [13], ofloxacin in two [17, 18], gatifloxacin in one [16], and ceftriaxone in two [20, 21]. Clinical responses in non-comparative trials were that 61 of 64 patients (95%) treated with azithromycin were afebrile within 7 days of therapy and were considered to be cured [14, 19].

Our study demonstrated that azithromycin is highly effective for the treatment of uncomplicated enteric fever in children. In this study, clinical cure was obtained in 98% of patients treated with azithromycin, whereas in ceftriaxone group, it was 86%. These findings were comparable with studies done by Wallace et al. [22] and Girgis et al. [23]. A study by Tribble et al. demonstrated that a 5-day course of azithromycin (20 mg/kg per day, with a maximum dose of 1000 mg/day) is effective against uncomplicated enteric fever in children and adolescents [24]. In our study, we used a low dose of azithromycin (10 mg/kg/day once a day) for 7 days and tried to compare with ceftriaxone (75mg/kg/day; maximum dose, 2.5 g/day) twice daily for 10 days. One of the reasons for this is to reduce the possible side effects related to the azithromycin usage [25].

Ceftriaxone is highly effective in the treatment of enteric fever but it is less than an ideal drug for its treatment. It shows a slow response with a mean time of 5-7 days or even longer to defervescence, which could be attributed to poor penetration capability of the drug into the cells, and thus difficult to eradicate the bacteria from the intracellular niche. Extended spectrum beta-lactamase (CTX-M-15 and SHV-12

ESBLs) and CMY-2-AmpC beta-lactamase producing *S. typhi* have been reported [26]. On the other hand, azithromycin possesses many characteristics for effective and convenient treatment of enteric fever in children with efficacy rate of more than 95% [27, 28]. However, treatment failure rates of 9.3% have been observed in earlier studies [29]. Two other studies have reported a clinical cure rate of only 82% and 92% [30, 31].

In this study we also found that most of the in vitro azithromycin resistant cases responded clinically. Outcomes of treatment were based on duration of defervescence, and development of complications. Regarding duration of defervescence, the average time of defervescence was 4.44 ± 1.25 days in azithromycin group. One previous study [30] showed the days of defervescence of azithromycin treatment 4.1 ± 1.1 days.

Study by Giris et al [32] found that the days of defervescence with azithromycin treatment was 3.8 ± 1.1 days. Response to treatment with azithromycin was excellent. Franck et al [30] found the cure rate 91% with azithromycin. They concluded that oral azithromycin administered once daily appeared to be effective for the treatment of uncomplicated typhoid fever in children and recommended that the agent could be a convenient alternative for the treatment of typhoid fever, especially in developing countries where medical resources are scarce. Once-daily oral treatment for 7 days (20 mg/kg/day) is convenient and should be favorable for out-patient compliance. Although parenteral azithromycin is available, it has not yet been popular in typhoid fever treatment.

Another study showed that Patients treated with ceftriaxone had a slightly shorter time to defervescence than did those treated with azithromycin (3.9 vs. 4.1 days, respectively); however, the difference was not significant, and both results were within time frames reported in previous typhoid treatment trials [19, 33-36]. Mild and transient gastrointestinal symptoms occurred in both treatment groups, but no adverse event was severe enough to require alteration in therapy [33-36].

CONCLUSION:

In conclusion, azithromycin given for 7 days at a dosage of 10 mg/kg/day (maximum dose, 500 mg/day) appears to be highly effective for the treatment of uncomplicated typhoid fever in children, with clinical cure rates comparable to those for ceftriaxone. Once-daily administration of oral azithromycin may offer a simple treatment regimen for typhoid fever caused by either susceptible or

drug-resistant strains of *S. typhi* and may be suitable for use in areas where medical resources are limited.

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