Original Article

Efficacy of Azithromycin versus Ceftriaxone for the treatment of uncomplicated typhoid fever in children

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ABSTRACT:

Introduction: *Typhoid fever is a global major public health problem. Its incidence is high in children from both low & high socio economic groups. Antimicrobial therapy is important in its management. MDR case has begun to appear around 1990. Ciprofloxacin resistance was first reported in Bangladesh in 2000.[6] Ceftriaxone is still highly effective, but costly and requires parental administration and cumbersome to children. So an effective, safe and alternative drug in the treatment of typhoid fever is always a demand. Azithromycin is a potential drug in treatment of typhoid fever because of its high intracellular penetration and long half-life (72 hours).* ***Aims & Objectives-*** *To determine the efficacy of Azithromycin versus Ceftriaxone in the treatment of uncomplicated typhoid fever.* ***Methodology-*** *This RCT was conducted in the Department of Paediatrics of Shaheed Mansur Ali Medical College & Hospital, Dhaka; over a period of 6 (six) months. A total of 35 cases (Azithromycin) & 35 controls (Ceftriaxone) were included in this study.* ***Results-*** *Most respondents in both groups were ≤ 5 years' age. Mean age was 5.53±3.41years for cases and 5.53±2.55 years for controls (p-0.146). In both groups M:F ratio was 1:1. Mean weight was 17.30±6.13 kg for cases and 17.17± 6.55kg for control (p-0.798). Most respondents were from middle socio-economic classes (p-0.083). Clinical presentation was similar in both groups. A quarter of participants in each group (25.7% & 22.9%) gave history of receiving antibiotic before admission. 'Widal test' was negative in 2.9% of cases and 5.7% of Control (p-0.328). S. typhi. was present in blood culture in majority cases except, 14.3% in Azithromycin and 8.6% in Ceftriaxone group yelled 'no growth' (p-0.241). Repeat blood culture on day10, showed no growth in all the 54 culture positive cases. Children of Azithromycin group was afebrile within 6 days of starting treatment, mean 4.88± 0.40 days and in Ceftriaxone group most (97.1%) required ≥7 days, mean 7.14±0.42 days (p-0.001). As defervescence was achieved before the completion of treatment, both the groups were discharged in due time, i.e. Azithromycin group after 7 days and Ceftriaxone group after 10 days.* ***Conclusion-*** *Treatment of uncomplicated typhoid fever with Azithromycin is relatively*

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easier; takes shorter time to achieve defervescence and the duration of treatment is also shorter in comparison to Ceftriaxone.
Key words: *Typhoid fever, Azithromycin, Ceftriaxone.*

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INTRODUCTION:

Typhoid fever is a systemic infection caused by bacterium salmonella enterica serotype typhi. It is a common febrile illness among the children of developing country and a global major public health problem. Almost 80% of the cases and deaths are in Asia & rests occur mostly in Africa.[1] High incidence of typhoid fever (>100/100000 case per year) include south central Asia and south East Asia, the existing estimate of the global burden of typhoid fever is 16 million illness and 6 lac deaths annually.[2] Its incidence is high in children from both low & high socio economic groups.[3] If left untreated the disease carries mortality rate up to 30%.[4] Hence antimicrobial therapy is important in its management. Previous first line drug in the treatment of typhoid fever were chloramphenicol, tetracycline, sulphonamide.[4]

Chloramphenicol has been the treatment of choice for typhoid fever for 40 years, but wide spread emergence of multi drug resistance (MDR) salmonella typhi resistant to Ampicillin, Chloramphenicol, Trimethoprime, Sulphamethoxazole, has necessitate the search for other therapeutic option.[5]

In Bangladesh typhoid fever is endemic due to defective sewerage system, unsafe water & food handling. Recent reports from Dhaka and Khulna reveal higher incidence of MDR *Salmonella typhi* infection with widely variable sensitivity pattern to commonly first line drugs.[6] MDR case begun to appear around 1990. Ciprofloxacin & Ofloxacine resistance was first reported in Bangladesh in 8% of enteric fever case in year 2000. In the year 2005 a resistance pattern of 70% was observed.[6] Fluroquinolones have proven to be effective, however to date they are restricted from routine use in children and quinolone resistant strain of *Salmonella typhi* have begun to be reported.[7]

Ceftriaxone and other 3rd generation cephalosporins are still highly effective against *S. typhi*, in addition to the high cost and requirement of parental administration, which is cumbersome and is an unpleasant experience for the children. Therefore, other regimens are required for the treatment of typhoid fever.

Azithromycin, a member of macrolide class of antibiotic, possesses many characteristics for effective and convenient treatment of typhoid fever. Including in vitro activity against many enteric pathogens, it has excellent penetration into most tissue, macrophage and neutrophil that are more than 100 fold higher than concentration in serum.[8] Previous studies have demonstrated that a seven days treatment course of Azithromycin was highly effective against uncomplicated typhoid fever in adult and children.[8] Azithromycin is a potential useful drug in treatment of typhoid

fever because of its high intracellular penetration and long elimination half life (72 hours). Azithromycin significantly reduce clinical failure and duration of hospital stay and reduce relapse.[9] Azithromycin appears to be an effective drug for treating uncomplicated typhoid fever in children with efficacy rate of more than 90%.[10]

Due to the emergence of MDR *S. typhi,* and resistance patterns varies in different regions, this study is focused on alternative drugs for its treatment and also to assess the efficacy of Azithromycin for typhoid fever in children of developing country. If Azythromycin is found to be effective in enteric fever it will be a glorious massage for us and will be a paramount significance for the clinicians to start empirical therapy in hospital as well as in private practice and also to reduce the duration of hospital stay. So the objective of the study was to determine the efficacy of Azithromycin versus Ceftriaxone in the treatment of uncomplicated typhoid fever.

METHODS AND MATERIALS:

This was a randomized controlled clinical trial, conducted at the Department of Paediatrics of Shaheed Mansur Ali Medical College & hospital, Dhaka, from June 2012 to December 2012, over 6 (six) months. Children 2-12 years old, admitted in the paediatric ward diagnosed as typhoid fever on the basis of clinical feature & investigation were the study population. A total of 70 children with enteric fever were included, and randomly divided by lottery in two groups, Group-A received oral Azithromycin and Group-B, were given intravenous Ceftriaxone. At the end of the study group A were taken as a case & group B as control.

Inclusion criteria was children of both sexes between 2-12 years, having fever for ≥7days & ≥2 of the symptoms, abdominal pain, hepatomegaly, splenomegaly or coated tongue with positive Widal test & or blood culture, parents of whom has given informed written consent. Children, whose parents didn't give written consent, who had history of allergy to Ceftriaxone/ Azithromycin, or children with major complication of typhoid fever like intestinal haemorrhage, perforation, shock etc. were excluded.

Group A, received Azithromycin 20 mg/kg/day in two divided oral doses for 7 days. Group B received inj. Ceftriaxone 100mg/kg/day I/V for 10 days. Repeated blood C/S were performed 10 days after initiation of treatment for those who were positive for *S. typhi.*

Data were collected by interview, physical examinations and laboratory investigations using a pre-tested structured questionnaire, and were processed and analyzed by statistical package for social science (SPSS) version 18. P value of <0.05 were taken statistically significant. Protocol of the study was approved by the IRB of Shaheed Mansur Ali Medical College & Hospital, Dhaka

RESULTS:

This study was undertaken with the objective to determine the efficacy of Azithromycin versus Ceftriaxone in the

treatment of uncomplicated typhoid fever. A total of 70 children, out of whom 35 were treated with Azithromycin (Group-A) & 35 with Ceftriaxone (Group-B), were included in this study.

Mean age of patients in Group-A (Azithromycin) was 5.53±3.41years and 5.53± 2.55 years in Group-B (Ceftriaxone) (p-1.0). Majority 20(57.1%) in Group-A and 18(51.4%) in Group-B were ≤ 5 years old, and 11(31.5%) & 15(42.8%) were between 5-10 years in Group-A and Group-B respectively. Rest were >10 years old, which was not significant (p-0.146). Interestingly about half of the participants in both groups, Group-A [17 (48.6%)] and Group-B [18 (51.4%)] were Males. Male: Female ratio was about 1:1. (p-0.691).

Mean weight of enrolled babies were 17.3±6.13kgs in Group-A and 17.171 ± 6.55kgs Group-B (p-0.929). Majority of them 24(68.5%) in Group-A and 23(65.7%) in Group-B were between 11-20kgs, and 3(8.6%) in Group-A & 4(11.4%) in Group-B were ≤ 10 kg weight. Eight (22.9%) in both groups were >20kgs weight, which was not significant (p-0.798).

Majority in Group-A 19(54.3%) from middle class, 12(34.3%) from lower class and rest were from upper class. In Group-B 14(40.0%) each were from middle and lower class and rest from upper class (p-0.083). Socio-economic classes based on monthly income (taka per month). Lower class: <10,000; Middle class: 10,000-40,000 and Upper class: >40,000.

Table-I: Distribution of the children by their presenting complaints

Complaints	Azithromycin (n=35) Percent	Ceftriaxone (n=35) Percent	Statistical calculations
Fever	100.0	100.0	RR=1; OR=NA
Immunization	97.1	97.1	RR=1.0; 95% CI: 0.9532-1.0491 OR=1.0; 95% CI: 0.1917-5.2165
Abdominal pain	25.7	31.4	RR=0.8185; 95% CI: 0.5263-1.2729 OR=0.7557; 95% CI: 0.4081-1.3992 χ^2 = 0.54; p-value = 0.462433
Diarrhoea	2.9	5.7	RR=0.5088; 95% CI: 0.1272-2.0351 OR=0.4941; 95% CI: 0.1168-2.0893
Constipation	14.3	20.0	RR=0.715; 95% CI: 0.3848-1.3286 OR=0.6674; 95% CI: 0.3172-1.4046 χ^2 = 0.78; p-value = 0.377141
GI bleeding	0.0	0.0	RR=NA; OR=NA
Rash	0.0	0.0	RR=NA; OR=NA

Cough	0.0	2.9	RR=0; 95% CI: 0-NA OR=0; 95% CI: 0-NA
Joint pain	0.0	0.0	RR=NA; OR=NA
Antibiotic before admission	25.7	22.9	RR=1.1223; 95% CI: 0.6873-1.8325 OR=1.1646; 95% CI: 0.6097-2.2244 χ^2 = 0.09; p-value = 0.764177
Coated tongue	100.0	88.6	RR=1.1287; 95% CI: 1.052-1.2109 OR=∞; 95% CI: NA-∞ χ^2 = 10.06; p-value = 0.001515
Hepatomegaly	97.1	97.1	RR=1.0; 95% CI: 0.9532-1.0491 OR=1.0; 95% CI: 0.1917-5.2165
Splenomegaly	45.7	65.7	RR=0.6956; 95% CI: 0.5383-0.8988 OR=0.4394; 95% CI: 0.2484-0.7772 χ^2 = 7.32; p-value = 0.006819
Joint swelling & tenderness	0.0	0.0	RR=NA; OR=NA
Toxic look	0.0	2.9	RR=0; 95% CI: 0-NA OR=0; 95% CI: 0-NA
Maculopapular rash	0.0	2.9	RR=0; 95% CI: 0-NA OR=0; 95% CI: 0-NA
Dehydration	0.0	2.9	RR=0; 95% CI: 0-NA OR=0; 95% CI: 0-NA
Abdominal tenderness	2.9	5.7	RR=0.5088; 95% CI: 0.1272-2.0351 OR=0.4941; 95% CI: 0.1168-2.0893
Abdominal distension	0.0	0.0	RR=NA; OR=NA
Total	100.0	100.0	

In both groups fever was present all (100.0%) participants. Most of the patients were immunized, 97.1% in both groups. Coated tongue, hepatomegaly, splenomegaly, abdominal pain and constipation were most notable presentations found among the participants with almost similar distribution between groups. About a quarter portion of participant in each group (25.7% & 22.9%) gave history of receiving antibiotic before admission.

Table-II: Distribution of the participants by their Widal test findings

Widal test	Azithromycin (n=35) Percent	Ceftriaxone (n=35) Percent	Statistical calculations
Positive	97.1 (34)	94.3 (33)	RR=1.0297; 95% CI: 0.9708-1.0922 OR=2.0293; 95% CI: 0.4886-8.5581 χ^2 = 0.953; p-value = 0.32895685
Negative	2.9 (1)	5.7 (2)	
Total	100.0	100.0	

***Inclusion criteria:** Positive Widal test & or blood culture

'Widal test' was negative in 2.9% of Azithromycin group and 5.7% of Ceftriaxone group [RR=1.0297; 95% CI:0.9708-1.0922; OR=2.0293; 95% CI: 0.4886-8.5581]. The difference was not statistically significant (p- 0.328).

Table-III: Distribution of the participants by the Blood culture findings

Blood culture	Azithromycin (n=35) Percent	Ceftriaxone (n=35) Percent	Statistical calculations
S. typhi	77.1 (27)	77.1 (27)	
No growth	14.3 (5)	8.6 (3)	χ^2 = 2.838; p-value = 0.24195585
#Not done	8.6 (3)	14.3 (5)	
Total	100.0	100.0	

#Not done due to refusal of the party and also

Inclusion criteria: Positive Widal test & or blood culture

Only microorganism found by blood culture was *S. typhi*.

At the end of treatment, repeated blood in all the 54 previously culture positive patients showed 'no growth'. Majority 30(85.7%) patients in Group-A become afebrile between 5-6 days after start of treatment and only 5(14.3%) became afebrile <5days. In Group-B majority 34(97.1%) become afebrile at ≥7days and only one patient became afebrile between 5-6 days. Mean period of defervescence was 4.88±0.40 days in Group-A and 7.14±0.42 days in Group-B, which is statistically significant (0.0001). As defervescence was achieved before the completion of treatment, both the groups were discharged in due time, i.e. Azithromycin group after 7 days and Ceftriaxone group after 10 days.

DISCUSSION:

This study was aimed to identify the efficacy of Azithromycin versus Ceftriaxone in the treatment of uncomplicated typhoid fever in a tertiary care hospital in Bangladesh. A total

of 35 cases (Azithromycin) & 35 controls (Ceftriaxone) were included in this study.

In both groups most of the respondents were in the '≤ 5 years' age group; 57.1% in Azithromycin and 51.4% in Ceftriaxone group. Mean age was 5.53±3.41years for Azithromycin group and 5.53±2.55 years for Ceftriaxone group (0.146). Frenck et al. enrolled total of 64 culture positive children (34 azithromycin recipients and 30 ceftriaxone recipients); mean age was 9.7 and 10.1 years respectively.[7] In another study by Frenck et al. 68 patients (32 of whom were in the azithromycin group) had *S. Typhi* isolated from cultures of blood or stool specimens; Age, mean years ± SD was 11.8 ± 3.6 and 10.8 ± 3.35.[8]

About half of the participants in both Azithromycin group [17(48.6%)] and Ceftriaxone group [18 (51.4%)] were Males. In both groups Male: Female ratio was about 1:1. (p-0.691). Frenck et al. found 20(58.8%) male in Azithromycin recipients and 17(56.7%) male among Ceftriaxone recipients; male:female ratio was 1.4:1 and 1.3:1.[7] Again, Frenck et al. in another study found 19(59.4%) male in Azithromycin recipients and 20(55.6%) male among Ceftriaxone recipients; male : female ratio was 1.46:1 and 1.25:1.[8]

More than two-third (68.5%) of the Azithromycin group and about two-third of the Ceftriaxone group (65.7%) weighted '11 to 20 kg'. Both groups showed similar Mean ± SD for weight (17.30±6.13) and (17.17±6.55) kgs. There was no statistically significant difference in distribution of weight among the groups (p-0.798). In both groups most respondents were from middle socio-economic classes. (p-0.083); which explains there was no significant statistical difference in the groups. Similarly Frenck et al. found, demographic and pretreatment laboratory evaluation of the subjects demonstrated that there were no significant differences between the treatment groups.[7] In another study by Frenck et al. analysis of demographic characteristics and results of pre-treatment laboratory tests revealed no statistically significant differences between patients treated with ceftriaxone and those treated with azithromycin.[8]

For both Azithromycin group and Ceftriaxone group fever was present in cent percent (100.0%) participants. Most of the patients were immunized, 97.1% in both groups. Coated tongue (100.0% & 88.6%), Hepatomegaly (97.1% & 97.1%), Splenomegaly (45.7% & 65.7%), Abdominal pain (25.7% & 31.4%) and Constipation (14.3% & 20.0%) were most notable presentations found among the participants. All the presentations showed similar distributions between the two groups and there was no significant statistical difference for any of the factor. Duration of fever before admission, mean days (range) was 9.7 (3–30) and 9.2 (3–15).[7] Fever duration before enrollment, mean days ± SD was 10.8±4.5 and 10.8±4.4 respectively.[8]

About a quarter portion of participant in each group (25.7% & 22.9%) gave history of receiving antibiotic before admission. 'Widal test' was negative in 2.9% of Azithromycin group and 5.7% of Ceftriaxone group [RR=1.0297; 95% CI: 0.9708-1.0922;

OR=2.0293; 95% CI: 0.4886-8.5581]. χ^2 calculated that the difference was not statistically significant (p-0.328). Only microorganism found by blood culture was *S. typhi*. About 14% culture report in Azithromycin group and 8.6% in Ceftriaxone group yielded 'no growth'. There was no statistically significant difference between the two groups (p-0.241). That implied that, pre-treatment evaluation of the subjects demonstrated that there were no significant differences between the two groups. 'Blood culture' findings of previously culture positive patients 10 days after starting of their treatment, out of 27 participants in each groups none (0.0%) was found to be positive. In other word, repeated blood culture in all the 54 previously culture positive patients showed 'no growth', means that, microbiological cure occurred in all (100%). At the Abbassia Fever Hospital cultures of blood specimens obtained from 64 children (34 azithromycin recipients and 30 ceftriaxone recipients) were positive for *S. typhi.* Demographic and pre-treatment laboratory evaluation of the subjects demonstrated that there were no significant differences between the two groups. Microbiological cure occurred in 33 (97%) of 34 patients treated with azithromycin versus 29 (97%) of 30 patients treated with ceftriaxone (*P* = NS).[7] At the same centre again 68 patients (32 in the azithromycin group) had *S.* Typhi isolated from cultures of blood or stool specimens obtained at enrolment and constituted the treatment group. Microbiological cure was achieved in every patient treated with azithromycin and in 35 (97%) of 36 patients treated with ceftriaxone (*P*-0.5).[8] In the present study all the patients were culture negative in both treatment groups at the end of treatment.

Children of the Azithromycin group became fever free within 6 days of starting their treatment; Mean ± SD (4.88±0.40) days and for the Ceftriaxone group most (97.1%) required ≥ 7 days; Mean ± SD (7.14±0.42) days, which was statistically significant (p-0.001). Khan et al.[11] found period of defervescence in Azithromycin group 5.48±1.24 days and in Ceftriaxone group 5.55±1.29 days. In another study by Khan et al.[12] periods of defervescence in Azithromycin group was 5.50±0.91 days and in Ceftriaxone group 5.33±1.09 days, which is similar to the present study. Similarly, in Cairo, Egypt responses to treatment were excellent in both groups. Patients responded quickly to therapy than the time required by our patients; the mean time to defervescence ±SD was 4.1±1.1 days and 3.9±1.0 days for azithromycin recipients and ceftriaxone recipients, respectively (*P*=NS).[7] Again in Cairo, Egypt both antibiotic therapies were highly effective. Mean time (± SD) to defervescence was 4.5 (±1.9) days for patients who received azithromycin and 3.6 (±1.6) days for patients who received ceftriaxone (*P* = NS).[8] The early response than ours, observed by this study may be explained by the fact that in our country, antibiotics are used and sold by unqualified persons at inadequate doses and duration, which is alarming.

As defervescence was achieved before the completion of treatment, both the groups were discharged in due time, i.e. Azithromycin group after 7 days and

Ceftriaxone group after 10 days. In Cairo, Egypt clinical cure occurred in 31 (91%) of 34 patients treated with azithromycin, compared with 29 (97%) of 30 patients treated with ceftriaxone (P = NS).[7] Again in Cairo, clinical cure was achieved in 30 (94%) of 32 patients treated with azithromycin and in 35 (97%) of 36 patients treated with ceftriaxone (P = 0.5).[8]

CONCLUSION:

From the present study it can be concluded that there is no significant difference in efficacy of Azythromycin and Ceftriaxone in treating uncomplicated Typhoid fever. Azythromycin took shorter duration to achieve defervescence, so the total duration of hospital stay was also shorter.

The present study reveals that Azythromycin and Ceftriaxone can be equally used in case of uncomplicated typhoid fever in children. But this was a small scale study done at a single centre over a brief period of time. A large scale, multi-centre study over long duration is required to verify the findings of the present study before recommending use of oral Azythromycin in treating uncomplicated typhoid fever in children.

This study was conducted in a tertiary care hospital in Dhaka city, in a small sample size of 70 patients, so the findings may not reflect the exact scenario of the country regarding typhoid fever.

REFERENCES:

1. Harish BN, Menezes GA, Sarangapani K, Parija SC. A case report & review of literature ciprofloxacin resistant salmonella enteric serover typhi in India. j Infect Developing countries 2008; 2:324-27.
2. Crump JA, Luby SP, Minpz DE. The global burden of typhoid fever. Bulletin of the Who Health Organization 2004, 82: 346-53.
3. Black RE, Cisneros L, Levine MM, Banfi A, Lobos H, Rodriguez H. Case control study to identify risk factor for paediatric endemic typhoid fever in Santiago, Chile. Bull WHO, 1985; 63:899-904.
4. Ferrera KP, Bonasang ES. Azithromycin versus first line antibiotics in the therapeutic management of documented case of typhoid fever. Phil j Microbiol Infect Dis 2004; 33: 163-68.
5. Girgis NI, Butler T, Frenck RW, Sultan Y, Brown FM, Tribble D and Khakhria R. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. Antimicrobial Agent and Chemotherapy, 1999; 43: 1441-44.
6. Rahman AKMM, Ahmad M, Begum RS, Ghosh AK, Hossain MZ. Multidrug resistant typhoid fever in children. J Dhaka Med Coll. 2008; 17: 121-26.
7. Frenck RW Jr., Nakhla I, Sultan Y, Bassily SB, Girgis YF, David J, et al. M Azithromycin versus Ceftriaxone for the Treatment of Uncomplicated Typhoid Fever in Children. Clinical Infectious Diseases 2000; 31:1134-38.

8. Frenck RW Jr. Mansour A, Nakhla I, Sultan Y, Putnams, Wierzba T, et al. Short course Azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. Clin infect Dis 2004; 38:951-7.

9. Shah D. Role of Azithromycin in enteric fever. Indian Pediatr 2009; 46:51-52.

10. Aggarwal A, Ghosh A, Gomber S, Mtra M, Prikh AO. Efficacy and Safety of Azithromycin for Uncomplicated Typhoid Fever: An Open Label Non-comparative Study. Indian Pediatr 2011; 48:553-56.

11. Khan KA, Biswas BC, Hossain I, Jahan I, Banu NA, Shamshad IA, Begum HA. Drug Response in Childhood Typhoid Fever: A Comparative Analysis of Ciprofloxacine, Ceftriaxone and Azithromycin. Sir Salimullah Med Coll J. 2012; 20: 36-44.

12. Khan KA**,** Rahman M, Nahar N, Mosleh T, Alam J, Banu NA, Hoque MM, Dutta S. A Comparative Analysis of Ceftriaxone and Azithromycin in the Treatment of Uncomplicated Typhoid Fever in Children. ICMH Journal. 2016; 7(1):33-39.