COMPARISON OF CLINICAL EFFECTIVENESS OF AZITHROMYCIN VERSUS CEFTRIAXONE IN TREATMENT OF ENTERIC FEVER IN PAEDIATRIC POPULATION

Saima Rafique, Shahzad Rasheed*, Munir Akmal Lodhi, Asad Maqbool Ahmad*****

PAF Hospital, Peshawar Pakistan, *Combined Military Hospital, Sialkot Pakistan, **Foundation University of Medical College, Islamabad Pakistan, ***Combined Military Hospital Peshawar Pakistan

ABSTRACT

Objective: To compare clinical effectiveness of azithromycin versus ceftriaxone in terms of mean time taken in number of days for defervesence in children with enteric fever.

Study Design: Quasi experimental study.

Place and Duration of Study: Pak Emirates Military Hospital Rawalpindi, from Oct 2015 to Apr 2016.

Methodology: The study involved 212 children of both genders aged between 2 to 12 years diagnosed with enteric fever. Patients were divided randomly into two treatment groups. All patients in group A were treated with oral azithromycin suspension/capsule (20mg/kilogram/day; max dose, 500mg/day) once daily for 7 days and group B with Intravenous (I/V) ceftriaxone (75mg/kg/day; max dose, 2.5 grams/day) twice daily for 10 days.

Results: No statistically significant difference was noted in the mean defervesence time in patients treated with azithromycin and ceftriaxone (4.48 ± 1.13 days vs. 4.32 ± 1.23 days; *p*=325). When stratified, there wasn't any significant difference in mean defervesence time in patients given azithromycin and ceftriaxone across age groups and genders.

Conclusion: There was no significant difference in mean defervesence time in patients given treatment for enteric fever with azithromycin versus ceftriaxone. A drug that was less invasive and has similar clinical effectiveness may be used as treatment alternative in pediatric patients with enteric fever.

Keywords: Azithromycin, Ceftriaxone, Clinical effectiveness, Enteric fever.

INTRODUCTION

Salmonella infections are an important public health problem worldwide[1]. The highest morbidity and mortality due to these infections lies among Infants, children, and adolescents in south-central and South-eastern Asia[1]. If not given proper treatment, enteric fever has a mortality of 30%, whereas appropriate antimicrobial treatment reduces mortality to as low as 0.5%[2]. While treating enteric fever, it is usually essential to initiate treatment before the laboratory sensitivity tests are available. Hence, it is important to know options (choice of antibiotic) and possible troubles before starting treatment[1].

The standard of care in treatment of typhoid fever in many parts of the world is Ceftriaxone, a third generation cephalosporin which is highly effective against *S. typhi*. However, due to parenteral administration of ceftriaxone, this antibiotic is less than an ideal treatment[3].

The use of azalide class of antibiotics has given another possible option for the treatment of typhoid fever. Azithromycin has in vitro activity against many enteric intracellular pathogens, including *S. typhi*. Clinical response of oral azithromycin is shown to be comparable to parenteral ceftriaxone with a mean defervesence time (days) of 3.82 ± 1.496 versus 3.3 ± 1.2 for ceftriaxone. Azithromycin decreases the treatment failure rate, length of hospital stay and relapse of enteric fever in comparison to ceftriaxone, when used in treating populations with MDR typhoid fever[4].

Cost and compliance, as well as safety and efficacy, are taken into consideration when choosing regimens for treating enteric fever in limited resources, disease endemic countries.

Correspondence: Dr Saima Rafique, House No. 181, Street No. 07, Askari-13, Adiala Road, Rawalpindi Pakistan

Email: drsaimajehanzeb@gmail.com

Received: 02 Apr 2018; revised received: 19 Apr 2018; accepted: 23 Apr 2019

The objective of this study was to compre the clinical effectiveness of ceftriaxone, which is the currently accepted drug used in treatment of acute typhoid fever with azithromycin. It has been found that due to its availability in oral form Azithromycin is a useful drug in treatment of typhoid fever and if found clinically effective in paediatric population may be used as a treatment alternative. We wanted to compare its clinical effectiveness (which will be calculated as mean time taken in terms of number of days for defervesence) in pediatric population also. Defervesence time will be taken as the number of day starting from initiation of therapy, patient took to become afebrile for a period of 24 hours.

METHODOLOGY

This was a quasi experimental study, was done at Pediatrics department, Pak Emirates Military Hospital, Rawalpindi for the period of 6 months from 5th October 2015 till 4th April 2016.

Sample size of 212 cases (106 in each group) was calculated with 80% power of test and 95% confidence level taking expected mean defervesence time as 3.82 ± 1.496 days after treatment with oral Azithromycin and 3.3 ± 1.27 days after treatment with I/V ceftriaxone in children suffering from enteric fever. Patients were selected by non-probability, consecutive sampling children of both genders aged between 2-12 years presenting with enteric fever which includes patients with high grade fever more than 101.60 f (≥38.60 C) of more than 3 days along with patient's typhidot showing IgM positive or Widal test showing (TH >1:160, TO 1:160) or blood culture positive for *S. Typhi.* were included in the study.

Patients allergic to ceftriaxone or azithromycin (on the basis of history). Patients presenting with complications of enteric fever (pneumonia, intestinal hemorrhage, perforation, shock or coma). Patients having acute tonsillitis, UTI, acute gastroenteritis, malaria or dengue fever (diagnosed on history, clinical examination and lab evaluation). Inability to swallow oral medication. Patients with heart disease, asthma requiring chronic medications, or immunodeficiency (diagnosed on history). Treatment within the past 48 hours with any medication e.g. Azithromycin, chloramphenicol, trimethoprim-sulphamethoxazole or ampicillin were excluded from the study.

Administrative permission from the concerned authorities and ethical committee were sought. Parents were explained about the risk and benefits of the study and informed written consent was obtained for the examination of children and intervention according to the guidelines of Helsinki Declaration. Permission was also obtained regarding use of data for research and publication.

All patients fulfilling the inclusion criteria were enrolled in the study and admitted to the inpatient department. Patients were randomly divided into group-A and group-B by lottery method.

All patients in group A were treated with oral azithromycin suspension/capsule (20mg/kg/day; max dose, 500mg/day) once a day for 7 days and group B with Intravenous (I/V) ceftriaxone (75mg/kg/day; max dose, 2.5 g/day) twice daily for 10 days. All medications were given in the hospital by trained nursing staff. The clinical response to the therapy of both drugs was calculated in terms of number of days taken for defervesence. However, if patient does not improve clinically after 7 days treatment with either ceftriaxone or azithromycin, he was managed with suitable second line medicines-medicines till his/her complete recovery and the drug was labeled non-effective. Data was recorded in predesigned proforma. Confidentiality of the patient record was maintained.

Numerical variables were presented by mean ± SD. Independent sample t-test has been applied to compare mean defervesence time between the groups taking *p*-value ≤0.05 as statistically significant. Categorical variable were presented by frequency and percentage. Post-stratification independent sample t-test and chi-square test has been applied taking *p*-value ≤0.05 as statistically significant.

RESULTS

Patient's age and gender stratification as shown in table-I. These patients were divided into two treatment groups randomly. Both the groups were comparable in terms of mean age (p=0.651), age groups (p=0.528) and gender distribution (p=0.888) as shown in table-II. There was in significant difference found in mean defervescence time in patients treated with azithromycin and ceftriaxone. When stratified, there was no significant difference in the mean defervesence time in patients treated with azithromycin and ceftriaxone across age groups as shown in table-III.

Table-I: Descriptive statistics of the study population.

Characteristics	Participants (n=212)
Age	7.25 ± 3.02 Years
Age Groups	
<5 Years	54 (25.5%)
≥5 Years	158 (74.5%)
Gender	
Male	131 (61.8%)
Female	81 (38.2%)

Table-II: Baseline characteristics of the study groups (n=106).

Characteristics	Azithromycin Group	Ceftriaxone Group	*p*-value
Age (yrs)*	7.16 ± 3.04	7.35 ± 3.02	
Age Groups			
<5 yrs	29 (27.4%)	25 (23.6%)	0.528
≥5 yrs	77 (72.6%)	81 (76.4%)	
Gender			
Male	65 (61.3%)	66 (62.3%)	0.888
Female	41 (38.7%)	40 (37.7%)	

*Independent sample t-test.

Table-III: Comparison of defervesence time between study groups (n=106).

Defervesence Time	Azithromycin Group	Ceftriaxone Group	*p*-value
Overall	4.48 ± 1.13	4.32 ± 1.23	0.325
Age Groups			
<5 yrs	4.48 ± 1.18	4.28 ± 1.34	0.557
≥5 yrs	4.48 ± 1.12	4.33 ± 1.20	0.428
Gender			
Male	4.48 ± 1.08	4.32 ± 1.34	0.453
Female	4.49 ± 1.23	4.33 ± 1.05	0.531

DISCUSSION

WHO recommends fluoroquinolones for the treatment of enteric fever without complications[6,7]. But these recommendations affects developing countries largely by increasing costs of treatment and an alarming rate of drug resistance[7]. Azithromycin has been shown as an alternative to parenteral ceftriaxone with a comparable mean defervesence time in a number of studies[9-11]. Its availability in oral form is additional advantage over ceftriaxone. However, these studies mainly involved adult population and there was limited data on its use in children with enteric fever.

The results of this study shows that there wasn't any significant difference in the mean defervesence time in patients given azithromycin and ceftriaxone (4.48 ± 1.13 vs 4.32 ± 1.23 days; p=0.325). A similar insignificant difference has also been reported in a number of previous studies by Islam *et al*. In 2014 (4.44 ± 1.25 vs 4.38 ± 1.21 days; p=0.794)[12]. Age of patients was from 2 years to 12 years with mean of 7.25 ± 3.02 years. A similar mean age of 7.3 years has been reported by Machakanur *et al*. (2014) in Indian children with typhoid fever[11]. There were 131 (61.8%) male and 81 (38.2%) female children. A similar male predominance has also been reported by Abdullah *et al*. In 2012 (58.06%)[13]. Majority (n=158, 74.5%) of children were over 5 years of age. Islam *et al*. (2014) similarly observed 78% of such patients to be above 5 years of age in Bangladesh[12]. The results of this study thus confirm that azithromycin is at least as effective as ceftriaxone in the treatment of enteric fever in children. It also has the added benefit of oral route which is more convenient in pediatric patients and allows patient management at home not necessitating admission only for administration of injectable treatment as in case of ceftriaxone. Furthermore, in a recent trial, Machakanur *et al*. In 2014 observed significantly lower mean defervescence time with azithromycin (2.72 vs 5.52 days; p=0.0) claiming it to be even superior to ceftriaxone[11]. In the light of above mentioned studies and the results of the present

study, it is advocated that azithromycin should be used as an alternative therapy in children presenting with enteric fever particularly in cases where admission is not otherwise required and child can be managed on outdoor basis[14-18].

A limitation to the present study is that we didn't carry out long term follow up of the patients for frequency of relapse of enteric fever in both groups. Future studies regarding comparison of prevention of enteric fever relapse between azithromycin and ceftriaxone are therefore recommended.

CONCLUSION

There was no significant difference in mean defervesence time in patients given treatment for enteric fever with azithromycin versus ceftriaxone, therefore a drug which is cost effective, less invasive and has comparable clinical effectiveness may be used as treatment alternative in pediatric population diagnosed with enteric fever.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

REFERENCES

1. Ahmed BH, Stanton K, Geme St, Behrman S. Enteric Fever (Typhoid Fever). Nelson's Textbook Pediatr 2015; 2(1): 1981388-92.
2. Arjyal A, Basnyat B, Koirala S, Karkey A, Dongol S, Agrawaal KK, et al. Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomized, controlled trial. Lancet Infect Dis 2011; 11(11): 445–54.
3. Trivedi NA, Shah PC. A meta-analysis comparing the safety and efficacy of azithromycin over the alternate drugs used for treatment of uncomplicated enteric fever. J Postgrad Med 2012; 58(2): 112-18.
4. Geetha VK, Yugendran T, Srinivasan R, Harish BN. Plasmid-mediated quinolone resistance in typhoidal Salmonellae: A preliminary report from South India. Indian J Med Microbiol 2014; 32(1): 31-34.
5. Butler T. Treatment of typhoid fever in the 21st century: promises and shortcomings. Clin Microbial Infect 2011; 17(7): 959-63.
6. Islam MN, Rahman ME, Rouf MA, Islam MN, Khaleque MA, Siddika M, et al. Multidrug resistant typhoid fever in children: a review. Mymensingh Med J 2007; 16(1): 149-53.
7. Hammad OM, Hifnawy T, Omran D, El Tantawi MA, Girgis NI. Ceftriaxone versus Chloramphenicol for Treatment of Acute Typhoid Fever. Life Sci J 2011; 8(2): 100-05.
8. Chandey M, Multani AS. A Comparative Study of efficacy and safety of azithromycin and ofloxacin in uncomplicated typhoid fever: a randomized, open labelled study. J Clin Diagn Res 2012; 6(10): 1736–39.
9. Nair BT, Simalti AK, Sharma S. Study comparing ceftriaxone with azithromycin for the treatment of uncomplicated typhoid fever in children of India. Ann Trop Med Public Health 2017; 10(1): 205-10.
10. Surojit Das, Ujjwayini Ray, Shanta Dutta. Revisit of fluoroquinolone and azithromycin susceptibility breakpoints for Salmonella entericaserovar Typhi. J Med Microbiol 2016; 65(7): 632–64.
11. Machakanur V, Krishnamurthy B. A clinical trial of treatment of uncomplicated typhoid fever: efficacy of azithromycin versus ceftriaxone. Int J Sci 2014; 2(6): 24-28.
12. Islam A, Mobarak R, Hasan AR, Hanif M. Clinical efficacy of azithromycin in typhoid and paratyphoid fever in children. J Enam Med Col 2015; 5(1): 34–38.
13. Abdullah FE, Haider F, Fatima K, Irfan S, Iqbal MS. Enteric fever in Karachi: current antibiotic susceptibility of Salmonellae isolates. J Coll Physicians Surg Pak 2012; 22(3): 147-50.
14. Agarwal Y, Gupta D, Sethi R. Enteric fever: Resurrecting the epidemiologic footprints. Astrocyte 2016; 3(3): 153–61.
15. Franco-Paredes C, Khan MI, Gonzalez-Diaz E, Santos-Preciado JI, Rodriguez-Morales AJ, Gotuzzo E. Enteric Fever: A Slow Response to an Old Plague. Public Library Sci Negl Trop Dis 2016; 10(5): e0004597.
16. Zorgani A, Ziglam H. Typhoid fever: misuse of Widal test in Libya. J Infect Dev Ctries 2014; 8(1): 680-87.
17. Meltzer E, Schwartz E. Enteric Fever: An Israeli perspective. Isr Med Assoc J 2007; 9(3): 736–41.
18. Mengist HM, Tilahun K. Diagnostic Value of widal test in the diagnosis of typhoid fever: a systematic review. Mengist and Tilahun, J Med Microb Diagn 2017; 6(1): 1-9.