Original Article

Comparison of the Clinical Effectiveness of Azithromycin Versus Ceftriaxone in Treatment of Enteric Fever

Hamidullah[1], Sami ul Haq[3], Iftikhar Ahmad[4] and Sadaqat Ali[2]

ABSTRACT

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

Study Design: Randomized Controlled Trial study

Place and Duration of Study: This study was conducted at the Department of Paediatrics, Hayatabad Medical Complex, Peshawar from November, 2015 to May, 2016.

Materials and Methods: A total of 140 patients were selected and divided into Group A and Group B by lottery method. Sampling technique was Non probability consecutive sampling. All patients in Group A were treated with oral azithromycin suspension/capsule (10mg/kg/day; maximum dose, 500mg/day) once daily for 7 days and Group B with Intravenous (I/V) Ceftriaxone (75mg/kg/day; maximum dose, 2.5 g/day) twice daily for 10 days.

All medications were administered in the hospital by nursing staff. The Clinical response to the therapy of both drugs were calculated in terms of number of days taken for defervescence. Data were recorded inpredesigned proforma by researcher.

Results: Overall Male to female ratio was 1.61:1. Sexdistribution 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 wasinsignificant 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

Citation of articles: Hamidullah, Haq S, Ahmad I, Ali S. Comparison of the Clinical Effectiveness of Azithromycin Versus Ceftriaxone In Treatment of Enteric Fever. Med Forum 2019;20(1):40-44.

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 estimated more than 22 million cases worldwide with 200,000 deaths every year have been reported.[1]

[1.] Department of Paediatrics / Pharmacist[2]. Khalifa Gulnawaz Teaching Hospital, Bannu, Khyber Pakhtunkhwa.

[1.] Department of Peads, Bannu Medical College & Khalifa Gulnawaz Teaching Hospital/Women & Children Teaching Hospital, Bannu,Khyber Pakhtunkhwa

[4.] Department of Peads, Mohtarma Benazir Butto SHaheed Medical Collge / DHQ Teaching Hospital, Mirpur AJK

Correspondence: Dr. Sami ul haq1, Assistant Professor, Department of Peads, Bannu Medical College & Khalifa Gulnawaz Teaching Hospital/Women & Children Teaching Hospital, Bannu, Khyber Pakhtunkhwa.
Contact No: 0333-5579218
Email: dr.samiulhaq@yahoo.com

Received: June, 2018
Accepted: September, 2018
Printed: January 2019

Chloramphenicol, Ampicillin, Sulfamethoxazole–Trimethoprim andTetracycline have been traditionally used in the therapy of Typhoid fever. After the resistance of chloramphenicol in 1970s, Quinolones were started as1st line treatment of typhoid fever in 1990s.[2] Due to the extensive usage of Quinolones, their susceptibility has decreased causing certain strainsbecoming resistant to them.[3]Ceftriaxone; a third generation cephalosporin, isa highly effective drug and among the most commonly drug used for thetreatment of uncomplicated and multi drug resistant typhoid fever. [4] Becauseof 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; firsttested 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 ± 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.[9]
Furthermore, there is no local data of Azithromycin efficacy versus Ceftriaxone, there is no research data available after 2004 to compare their Efficacy and Ceftriaxone is still used as 1st line drug in outdoor patients. We want to compare both the drugs so that better one could be recommended in future.

MATERIALS AND METHODS

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.
One Hundred& 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 ifpatient is 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 proforma by researcher.
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 for7 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 Awhile 42(60%) were male and 28(40%) were female belonging to Group B.This 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 contains25(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 theage of more than 11 years of age. While group B have average age of 5.42years +2.35SD and contains 25(35.7%) patients in less than or equal to 4years, 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 was5.47 years +2.38SD. The age distribution among the group was insignificant with p-value 0.791.
Defervescence wise distribution shows that Group A have average defervescence of 4.39days + 1.12SD while in Group B it was 4.46days+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 2)When defervescence was stratified among the age over both the group itwas shown that age group were insignificant defervescence in both the groups.
Similarly, when defervescence of the patients were stratified amonggender it shows that gender has also insignificant effect in both the groups.

Table No.1: Gender distribution in both the groups:

Gender	Groups		Total	p-value
	Group A	Group B		
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: Comparison of defervescence and weight in both the groups.

Groups	Number of patients	Mean	Std. Deviation	p-value
Group A	70	4.3857	1.12021	0.693
Defervescence (in days) Group B	70	4.4571	1.01704	
Group A	70	15.4857	6.91091	0.823
Weight (in kg) Group B	70	15.2286	6.64890	

DISCUSSION

Enteric fever is a potentially fatal multisystem illness caused by Salmonellatyphi or Salmonella paratyphi.[10] It occurs worldwide where water supply andsanitation are substandard.[11] 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.[12,13,14]

Azithromycin was tested in the 1990s, with good results, and can now be regarded as a promising alternative to fluoroquinolones and cephalo-sporins.[15,16,17]

Nine prospective clinical trials employing azithromycin that enrolled culture-positive children and adults with typhoid fever were carried out inEgypt, India, Vietnam, and Bangladesh.[18,19]The drug was received by a total of 453 patients, of whom 268 (59%) were children. Its dosage was 10 or 20mg/kg/day for children and 500 mg/day or 1 g/day for adults, given orally for7 days in seven trials and for 5 days in two trials. Two trials were notComparative.[15, 20]whereas randomized assignments were made to different comparator drugs in the remaining trials: chloramphenicol in one[16], Ciprofloxacin in one[14], ofloxacin in two[18,19], Gatifloxacinin one[17], and ceftriaxone in two [21,22]. Clinical responses in non-comparative trials were that61 of 64 patients (95%) treated with azithromycin were a febrile within 7 days of therapy and were considered to be cured. [15,20]

Our study demonstrated that azithromycin is highly effective for the treatmentof uncomplicated enteric fever in children. In this study, clinical cure wasobtained 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.[23] and Girgis et al.[24]

A study by Tribble et al. demonstrated that a 5-day course of azithromycin (20mg/kg per day, with a maximum dose of 1000 mg/day) is effective against uncomplicated enteric fever in children and adolescents.[25] In our study, weused 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 possibleside effects related to the azithromycin usage.[26]

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.[27] On the other hand, azithromycinpossesses many characteristics for effective and convenient treatment of enteric fever in children with efficacy rate of more than 95%.[28,29]. However, treatment failure rates of 9.3% have been observed in earlier studies.[30] Twoother studies have reported a clinical cure rate of only 82% and 92%.[31,32] 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 inazithromycin group. One previous study104 showed the days of defervescence of azithromycin treatment 4.1 ± 1.1 days. Study by Giris et al [33] 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 [31] 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 forout-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 trials93.[34-37] Mild and transient gastrointestinal symptoms occurred in bothtreatment groups, but no adverse event was severe enough to require alteration in therapy.[34-37]

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 treatmentof uncomplicated typhoid fever in children, with clinical cure ratescomparable to those for ceftriaxone. Once-daily administration of oralazithromycin may offer a simple treatment regimen for typhoid fever causedby either susceptible or drug-resistant strains of S. typhi and may be suitablefor use in areas where medical resources are limited.

Author's Contribution:

Concept & Design of Study:	Hamidullah
Drafting:	Sami ul Haq
Data Analysis:	Iftikhar Ahmad, Sadaqat Ali
Revisiting Critically:	Hamidullah, Sami ul Haq
Final Approval of version:	Hamidullah

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Kariuki S, Revathi G, Kiiru J, Mengo DM, Mwituria J. Typhoid inKenya is associated with a dominant multidrug-resistant Salmone llaentericaserovar Typhi haplotype that is also widespread in Southeast Asia. J Clin Microbiol 2010;48:2171–6.
2. Capoor MR, Nair D. Quinolone and cephalosporin resistance in enteric fever. J Global Infect Dis 2010;2:258-62.
3. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis 2010;50(2): 241-6.
4. Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries 2011;5(5): 324–37.
5. Capoor MR, Rawat D, Nair D, Hasan AS, Deb M, Aggarwal P, et al. In vitro activity of azithromycin, newer quinolones and cephalosporinsin ciprofloxacin resistant Salmonella causing enteric fever. J Med Microbiol 2007;56:1490-4.
6. Butler T. Treatment of typhoid fever in the 21st century: promises and Shortcomings. Clin Microbiol Infect 2011;17:959–63.
7. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). Cochrane Database Syst Rev 2008; 4:CD006083
8. Frenck RW Jr, Mansour A, Nakhla I, Sultan Y, Putnam S, 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. Christie AB. Infectious Diseases: Epidemiology and Clinical Practice.4th ed. Edinburgh, Scotland: Churchill Livingstone;1987.
10. Bhutta ZA. Enteric fever. In: Behrman RE, Kliegman RM, Jenson HB,(Editors).Nelson Textbook of Pediatrics. First South Asia Edition, Philadlphia PA: Saunders Publishers;2015.p. 1388-93.
11. Park K. Park's Textbook of Preventive and Social Medicine, 23rd ed. Jabalpur: M/S Banarsidas Bhanot; 2015.p.234-8.
12. World Health Organization. 6th International Conference on Typhoid Fever and other Salmonellosis, Geneva, WHO; 2006.
13. Crump JA, Stephen P, Luby ED. The global burden of typhoid fever.Bull World Health Organ. 2004;82(5):1-24.
14. Girgis NI, Butler T, Frenck RW. Azithromycin versus ciprofloxacinfor treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. Antimicrob Agents Chemother 1999;43:1441–4.
15. Tribble D, Girgis N, Habib N, Butler T. Efficacy of azithromycin for typhoid fever. Clin Infect Dis 1995;21:1045–6.
16. Butler T, Sridhar CB, Daga MK. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India. J Antimicrob Chemother 1999;44:243–50.
17. Dolecek C, La TTP, Rang NN. A multi-center randomized controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. PLoSONE 2008;3:e2188.
18. Chinh NT, Parry CM, Ly NT. A randomized controlled comparison of azithromycin and of loxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. Antimicrob Agents Chemother 2000;44:1855–9.
19. Parry CM, Ho VA, Phuong LT. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin–azithromycin combinationfor treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. Antimicrob Agents Chemother 2007;51:819–25.
20. Islam MN, Rahman ME, Rouf MA, et al. Efficacy of azithromycin inthe treatment of childhood typhoid fever. Mymensingh Med J 2007;16: 149–53.
21. Frenck RW, Nakhla I, Sultan Y, et al. Azithromycin versus Ceftriaxonefor the treatment of uncomplicated typhoid fever in children. ClinInfect Dis 2000;31:1134–8.
22. Frenck RW, Mansour A, Nakhla I. Short-course azithromycin for the treatment of uncomplicated typhoid fever in children and adolescents. Clin Infect Dis 2004;38:951–7.
23. Wallace MR, Yousif AA, Mahroos GA, Mapes T, Threlfall EJ, RoweB, et al. Ciprofloxacin versus ceftriaxone in the treatment of multi-resistant typhoid fever. Eur J Clin Microbiol Infect Dis 1993;12(12):907-10.
24. Girgis NI, Sultan Y, Hammad O, Farid Z. Comparison of the efficacy, safety and cost of cefixime, ceftriaxone and aztreonam in the treatment of multidrug-resistant Salmonella typhi septicemia in children. Pediatr Infect Dis J 1995; 14(7):603-5.
25. Tribble D, Girgis N, Habib N, Butler T. Efficacy of azithromycin for typhoid fever. Clin Infect Dis 1995;21(4):1045-6.
26. Bhutta ZA. Enteric fever. In: Behrman RE, Kliegman RM, Jenson HB,(Editors).Nelson Textbook of Pediatrics. First South Asia Edition, Philadlphia, PA: Saunders Publishers; 2015.p. 1388-93.
27. Gokul BN, Menezes GA, Harish BN. ACC-1 beta-lactamase producing Salmonella enteric Serovartyphi, India. Emerg Infect Dis 2010; 16(7):1170-1.
28. 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):112-8.
29. Rai S, Jain S, Prasad KN, Ghoshal U, Dhole TN. Rationale of azithromycin prescribing practices for enteric fever in India. Ind J Med Microbiol 2012; 30(1):30-3.
30. Parry CM, Ho VA, Phuong le T, Bay PV, Lanh MN, Tung le T, et al. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multi drug resistant and nalidixic acid-resistant typhoid fever. Antimicrob Agents Chemother 2007;51(3):819-25.
31. Frenck RW Jr, Nakhla I, Sultan Y, Bassily SB, Girgis YF, David J, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. Clin Infect Dis 2000; 31(5):1134-8.
32. Rakita RM, Jaques-Palaz K, Murray BE. Intracellular activity of azithromycin against bacterial enteric pathogens. Antimicrob Agents Chemother 1994;38(9):1915-21.
33. Girgis NI, Butler T, Frenck RW, Sultan Y, Brown FM, TribbleD. Azithromycin versus ciprofloxacin for the treatment of uncomplicated typhoid fever that included patients with multi drug resistance. Antimicrob Agents Chemother 1999;43:1441–4.
34. Smith MD, Duong NM, Hoa NT. Comparison of ofloxacin and ceftriaxone for short-course treatment of enteric fever. Antimicrob Agents Chemother 1994;38:1716–20.
35. Cao XT, Kneen R, Nguyen TA, Truong DL, White NJ, Parry CM. A comparative study of ofloxacin and cefixime for treatment of typhoid fever in children. Dong Nai Pediatric Center Typhoid Study Group. Pediatr Infect Dis J 1999;18:245–8.
36. Van den Bergh ET, Gasem MH, Keuter M, Dolmans MV. Outcome in three groups of patients with typhoid fever in Indonesia between 1948 and 1990. Trop Med Int Health 1999;4:211–5.
37. Dutta P, Rasaily R, Saha MR. Ciprofloxacin for treatment of severe typhoid fever in children. Antimicrob Agents Chemother 1993;37:1197–9.