

Comparison of Oral Azithromycin and Intra Venous Ceftriaxone for Treatment of Uncomplicated Enteric Fever in Children

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Abstract

Background : To compare the clinical efficacy of intravenous (I/V) Ceftriaxone with oral Azithromycin in 2-12 year old children diagnosed with enteric fever.

Methods: In this comparative study children with the history of fever for >4 days and at least two out of these findings, i.e., toxic physical appearance, abdominal pain, coated tongue, hepatomegaly, splenomegaly were divided into two equal groups. Patients in Group A were given Azithromycin 20 mg / kg/ day as a single oral dose whereas patients in Group B were given Ceftriaxone 100 mg/kg/day as a single I/V injection for 07 days. Before initiation of therapy samples for Typhidot and Widal test were collected and only those testing positive were included.

Results: There were 42 (93.3%) and 40 (88.9%) patients in both the groups respectively who were clinically cured. No significant difference was found between these two groups (p-value 0.459).

Conclusion: There was no difference in the clinical efficacy between Ceftriaxone and Azithromycin for the treatment of typhoid fever in children.

Key Words: Typhoid fever, Salmonella Typhi, Antibacterial agents, Febrile illness

Introduction

Enteric fever is a fatal multi-systemic illness caused by a gram-negative bacterium Salmonella typhi and Paratyphi. It is one of the major public health burden.^{1,2} The global estimate of incidence of enteric fever is 26.9 million cases annually, out of which 1 % result in death.³ The highest incidence is in South Central and South East Asia (100/100,000 cases/year) with the highest burden in children aged 2 - 15 years. Annual typhoid rates in recent studies from India, Pakistan & Indonesia range from 149 to 573 cases per

100,000 children.⁸ Poor sanitary conditions and overcrowding favor its growth. Its route of transmission is faeco-oral.^{4,7}

Its classical presentation is high grade fever, headache, malaise, anorexia, abdominal pain, constipation or diarrhea and maculopapular rash (rose spots) on the trunk lasting for 2-5 days in 25% of cases.⁹ Serious complications may develop in up to 10% cases during third week of illness such as intestinal hemorrhages and perforation, meningitis, pneumonia, myocarditis, DIC, thrombocytopenia, encephalomyelitis, psychosis, hepatitis, haemolytic uremic syndrome and Guillain-Barre syndrome.^{9,10} Mortality rate of enteric fever is <1% but it is high if treatment is delayed.¹¹ Therefore antimicrobials have the prime role in its management.

Because of the irrational use of antibiotics, over the counter medicines and the resultant emergence of resistance, its treatment is becoming difficult.¹⁰ Previously Chloramphenicol, Ampicillin and Cotrimoxazole were used for its treatment. In 1980 emergence of resistance to these first line drugs [defined as multidrug resistance (MDR)] limited their use.^{9,12,13} MDR strains were first reported from Asia and Middle East and later from all over the world.¹⁰

Nowadays, widespread use of Fluoroquinolones led to the development of quinolones resistant strains.¹² Recent studies done in India showed increasing resistance to Ceftriaxone as well.^{14,15} For this reason, it is necessary to search for new antibiotic options for enteric fever.

The recommended first line treatment for Enteric fever is Third generation Cephalosporins, for uncomplicated cases oral Cefixime or Cefpodoxime and for complicated cases I/V Ceftriaxone, Cefotaxime, or Cefoperazone.⁹ Recent studies showed that for Ceftriaxone resistant strains, Azithromycin has good efficacy with safety.^{12,16,17} It is recommended in a dose of 20 mg/kg/day (maximum -1000 mg/day) for 7 days.^{12,17} Various studies have shown clinical cure

of 94%-96% for Azithromycin compared with 27% for Ceftriaxone. ^{18,19}

Prompt treatment of Enteric fever drastically reduces the complications and mortality. We use both Azithromycin and Ceftriaxone for treatment of typhoid fever in our population.

Patients and Methods

This randomized controlled trial was conducted in Department of Paediatrics, Railway Hospital and Islamic International Medical College, from January to July 2016. Sample size was approximately equal to 45 patients in each group. Group A comprised patients on Oral Azithromycin and Group B comprised patients on intravenous Ceftriaxone. Inclusion criteria was children between 2 and 12 years of age of either sex with enteric fever. Exclusion criteria were children who have taken treatment for their illness, who had allergy to Ceftriaxone or Azithromycin (other macrolides), who were unable to swallow oral medications and with complications like gastrointestinal haemorrhage; intestinal perforation or shock. Typhoid Fever was defined as temperature >38.5 C and a history of fever for at least 04 days plus at least two of the following criteria: toxic physical appearance (like pallor, lethargy, irritability, (>16 beats / min > 100 beats /min) tachypnea, abdominal pain, coated tongue, hepatomegaly (on clinical examination), splenomegaly (on clinical examination) with a positive Widal test (TO titer equal or > 160 with TO > TH) or a positive Typhidot test. Clinical Cure (Efficacy) was defined as clinical improvement and resolution of all symptoms by the end of seven days of therapy. Patients enrolled in the study were hospitalized for the entire treatment period and 3 days after completion of therapy. Group A patients were given Azithromycin 20mg/kg/day as single oral dose for 07 days. Group B patients were given Ceftriaxone 100mg/kg/day as single I/V injection for 07 days. During hospital stay, vital signs were monitored 8 hourly, and patients were examined daily to assess the effectiveness of treatment. Chi-square test was used to compare efficacy in both the groups. P value <0.05 was significant. Effect modifiers like age and gender were controlled by stratification. For Post stratification Chi-square test was applied and a value ≤ 0.05 was taken as level of significance.

Results

Mean age (years) in the study was 6.97±3.01 with ranges from 02 to 12 years. There were 47 (52.2%) male and 43 (47.8%) female patients. Majority (91.1%) were

cured from symptoms of typhoid by the end of seven days of therapy (Table 1). Majority (93.3) were symptom free at the end of 07 days who received Azithromycin whereas 40 (88.9) patients were cured with Ceftriaxone (p-value 0.459; Table 2). There were 22 (91.7) and 19 (82.6) male patients in both the groups respectively who were clinically cured which was statistically not significant (p-value 0.352). Similarly, efficacy in female patients in both the groups was statistically not significant (p-value 0.973; Table 3). In children of 2-6 years azithromycin was effective in 92% cases while ceftriaxone showed 95% efficacy as compared to children of 7-12 years age in whom azithromycin was more efficacious (95%) than ceftriaxone (84%) (Table 4).

Table 1: Frequency and percentage of Clinical Cure (efficacy)

	Frequency	Percentage
Achieved	82	91.1
Not achieved	08	8.9
Total	90	100.0

Table 2: Comparison of Clinical Cure (efficacy) in both the groups

Clinical cure (efficacy)	Azithromycin Group (Oral)	Ceftriaxone Group (I.V)	p-value
Achieved Number (%)	42(93.3)	40(88.9)	0.459
Not achieved Number (%)	3(6.7)	5(11.1)	

Table 3: Effect modifier like gender stratification with efficacy in both the groups

Gender	Clinical Cure (Efficacy)	Azithromycin Group (Oral)	Ceftriaxone Group (I.V)	p-value
Male	Achieved Number (%)	22(91.7)	19(82.6)	0.352
	Not achieved Number (%)	2(8.3)	4(17.4)	
Female	Achieved Number (%)	20(95.2)	21(95.5)	0.973
	Not achieved Number (%)	1(4.8)	1(4.5)	

Table 4: Effect modifier like Age stratification with Efficacy in both the groups

Age Group	Clinical Cure (efficacy)	Azithromycin Group (Oral)	Ceftriaxone Group (I.V)	p-value
2 - 6 years	Achieved Number (%)	23(92.0)	19(95.0)	0.688
	Not achieved Number (%)	2(8.0)	1(5.0)	
7 - 12 years	Achieved Number (%)	19(95.0)	21(84.0)	0.243
	Not achieved Number (%)	1(5.0)	4(16.0)	

Discussion

Enteric fever is a major health problem in developing countries like Pakistan but now it's becoming a global health concern because of the emergence of resistant strains of Salmonella typhi and paratyphi. Resistance has been documented with most of the first line drugs like cephalosporins and quinolones.²⁰ Few studies reported that Azithromycin is highly effective in uncomplicated Enteric fever in adults and children.²¹ In our study, mean age (years) in the study was 6.97±3.01 with ranges from 02 to 12 years. In a study conducted by Hussain et al, mean age in years was 6.09±3.09 and in the study conducted by Aggarwal et al it was 7.5 years.^{22,23} A study in 2012 observed that the frequency and percentage of male patients was 33(55) and female patients was 27(45.0).²¹ The study conducted in India observed 93.5% males.²³ In our study, there were 47 (52.2) male and 43 (47.8) female patients. In our study, out of 90 patients, there were 82 (91.1%) patients who were cured by the end of seven days of therapy. Whereas in a study conducted in 2012, there were 49(98%) patients who had a complete cure.²¹

In present study while comparing clinical cure (efficacy), there were 93.3% patients who were cured by Azithromycin whereas 88.9% patients were cured by Ceftriaxone. While in a study conducted by Machakanuret al, the cure rates were 96% in patients treated with Azithromycin compared with 27% of patients who received I/V Ceftriaxone.²⁴ A study, conducted in 2012, showed Azithromycin to be effective in 94.6% patients.²² A non-comparative study conducted in India revealed that azithromycin was effective in 90% of the patients.²³ Two more studies revealed the efficacy of Azithromycin to be 82 & 92%.^{25,26}

The sensitivity to ceftriaxone was 100 % in 2 studies conducted in India in 2000 and 2005 while we found the sensitivity to be 88.9%.^{27,28} A meta-analysis of 20 prospective clinical trials revealed Azithromycin to be a better choice as compared to other antibiotics being commonly used while our study showed no difference of efficacy between Ceftriaxone and Azithromycin.²⁹ Our results were closer to another study conducted in Dhaka in 2009 which showed Azithromycin effectiveness to be 94% while ceftriaxone was 97.9%.³⁰ Both studies showed Azithromycin and Ceftriaxone to be highly effective in uncomplicated typhoid fever.

Conclusion

There is no difference of clinical efficacy among Ceftriaxone and Azithromycin for the treatment of uncomplicated typhoid fever in children.

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Key for Contribution of Authors : A= Conception/ Study/ Designing /Planning; B= Experimentation/Study conduction; C=Analysis/Interpretation/ Discussion; D= Manuscript writing; E= Critical review; F= Facilitated for reagents/Material/ Analysis