AZITHROMYCIN VERSUS CEFTRIAXONE- WHICH IS BETTER IN UNCOMPLICATED TYPHOID FEVER? A CLINICAL TRIAL IN A TERTIARY CARE HOSPITAL

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ABSTRACT

BACKGROUND

Enteric fever has been very a common and many times a fatal infective disease found in developing countries and has been known to have increasing resistance to novel drugs. So, there is an urgent need for a simple, therapeutic, cost-effective medicine to treat typhoid fever & to prevent further drug resistance.

METHODS

It is a non-randomized, case-control study done in Paediatrics department of Dr. Prabhakar Kore Hospital & Research centre of KAHER (KLE Academy of Higher Education and Research), attached to J N Medical College, Belagavi, over a period of 18 months from June 2017 to December 2018. The study included 200 children (2-17 years of age) with positive Widal result, uncomplicated-enteric fever; in this cohort, 100 children were treated using (oral, low dose, for short duration of 6 days) Azithromycin and remaining 100 children were treated with (intravenous, 7 days) Ceftriaxone. Each child was assessed clinically every day, & study results were captured as clinical and microbiological cure or failure, at the end of either drug regimens. This descriptive data was statistically analysed in SPSS-20.0 software. The p-value of <0.05 was taken as significant statistically.

RESULTS

Periods required by children for responding to drug therapy and to become afebrile i.e., defervescence were significantly ($p=0.000$) less with Azithromycin receiving group than ceftriaxone receiving group. 95% of children who received azithromycin showed defervescence by 5th day of regimen but, only 29% of children receiving ceftriaxone attained defervescence by 5th day of regimen. There was no microbiological clearance at 10th day in only one case of ceftriaxone trial-group. Significantly ($p=0.027$) there was early clinical cure in azithromycin trial group as compared to ceftriaxone trial group. The microbiological cure was not comparable in either groups ($p=0.135$).

CONCLUSION

At the end we come to the conclusion that oral Azithromycin (10 mg/kg/day, once a day for 6 days) is more efficacious in uncomplicated-typhoid fever management as compared to intravenous ceftriaxone (100 mg/kg/day in 2 divided doses for 7 days) in children and adolescents of 2 to 17 years age group.

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BACKGROUND

Enteric fever caused by *Salmonella typhi* and *paratyphi* has been a very common and often fatal disease in children of developing countries. There is an incidence of 500 cases/lakh population (0.5%) and a high mortality rate.^{1,2} As per the World Health Organization at least 12.5 million cases of typhoid are diagnosed worldwide annually.^{3,4}

For many decades, chloramphenicol has been drug of choice for enteric fever.⁵ But it is also found that many resistant strains have been emerging recently. Thus, there is need for any other treatment options.⁶

Fluoroquinolone resistant strains of *Salmonella typhi* have been isolated & documented. Ceftriaxone (A 3rd

generation cephalosporin) is highly effective in enteric fever; but every time it is supposed to be administered parenterally; hence, considered as lesser ideal treatment option in enteric fever.

Many studies have shown that the azithromycin concentration in neutrophils are more than 100-fold the serum level. It is also recently found that azithromycin given once daily appears to be helpful in treatment of typhoid-fever.⁷ If these results are confirmed, in developing countries where in resources are limited, oral azithromycin could be a convenient alternative drug for the treatment of typhoid fever.

Therefore, we hereby provide a simple study for a clinically effective drug in treatment of typhoid fever (Uncomplicated): comparing oral Azithromycin with intravenous Ceftriaxone.

METHODS

A sum of 200 Widal positive uncomplicated typhoid fever children were considered for this study in age group of 2-17 years who were admitted in the paediatric department of Dr Prabhakar Kore Hospital & Research of KAHER, attached to J. N. Medical College, Belagavi, over a period of 18 months June 2017 to December 2018.

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All these were enrolled in the study with their parents' consent. Each child was enrolled in separate proformas including the demographic data, chief complaints, associated symptoms, WIDAL test titres, and temperature recordings. This cohort was divided into 2 equal groups: Azithromycin receiving group (Receiving 10 mg/kg/day, orally, once day for 6 days) and Ceftriaxone receiving group 100 mg/kg/day, intravenous, in 2 DD for 7 days) as a basic treating drug for typhoid. Investigations done were: complete blood count, blood-culture (On day 1 and day 10 to correlate the treatment outcomes- clinically and microbiologically) using the standardised culture-method (XLD-agar).

Each patient was examined clinically, evaluated and proforma was updated and some data was captured (Appetite, headache, temperature (Axillary), abdominal-pain, constipation/diarrhoea, hepatomegaly, and splenomegaly). Adverse reactions of Azithromycin and Ceftriaxone were searched for and if present, the drug was replaced by a safer alternative & subsequently the patient was excluded from this study. Patients were receiving in-patient care for entire treatment period and the study result was captured as clinical and microbiological cure and failure respectively. This data was analysed as Contingency co-efficient or Chi-square test, Independent samples 't' test using the SPSS-20.0 software. <0.05 p-value was considered statistically significant.

RESULTS

Total 200 patients in male: female ratio of 1.2:1 with positive WIDAL were enrolled in the study at admission to hospital. The mean age of subjects of azithromycin receiving group was 7.3 years & that for ceftriaxone receiving group was 8.6 years. The male: female ratio was 1.02:1 in azithromycin receiving group & 1.1:1 in ceftriaxone receiving group.

Symptoms and Signs

There was no significant difference between the two drug receiving children with respect to demographic data & pre-treatment laboratory results. Fever was the chief complaint in all these cases (With a mean duration of 9.36 days in azithromycin receiving group; 10.5 days in ceftriaxone receiving group).

Laboratory Parameters Comparison

The mean haemoglobin in Azithromycin trial group was 12.2 gm/dL and for ceftriaxone trial group was 11.16 gm/dL. The mean total leucocyte count was 6, 134/cu mm in Azithromycin trial group whereas in ceftriaxone trial group it was 5, 609/cu mm. the mean platelet count was 2.16 lakh/ cu mm in azithromycin trial group as compared to 3.8 lakh/cu mm in ceftriaxone receiving group. The Leucopenia (WBCs <4000/cu mm) was documented in only 28% of Azithromycin receiving group and 22.2% of ceftriaxone receiving group.

Daily Monitoring & Evaluation Comparison (Table 1)

Number of days taken to become afebrile i.e., defervescence was significantly less with azithromycin receiving group as compared with Ceftriaxone receiving group, also it was statistically significant (p=0.000).

The mean defervescence time was 2.72 days in azithromycin receiving group and 5.52 days in ceftriaxone receiving group. On 5th day of hospitalization, patients receiving azithromycin showed 95% defervescence whereas patients receiving ceftriaxone had defervescence only in 29% cases-

- One of the presenting symptoms was diarrhoea which responded well in azithromycin treatment group (100% by 3rd day) better than ceftriaxone treatment group (92% by 3rd day) (p=0.002).
- Anorexia which was one of the symptoms was relieved by 3rd day in 96% of cases treated using azithromycin but only 56% of cases treated using ceftriaxone; it was statistically significant (p=0.001).
- Coated-tongue was a common sign found in typhoid, was cleared early with azithromycin treatment as compared to ceftriaxone treatment but was not found to be statistically significant (p=0.2).
- There were no adverse reactions observed in both the study groups.
- The patient compliance to take azithromycin was better as compared to intravenous ceftriaxone

Blood-Culture Comparison

- The blood culture yield was 12% in this study.
- Five out of 100 (5%) azithromycin received patients and seven out of 100 (7%) ceftriaxone received patients had positive blood culture of salmonella organisms. This blood culture was done on 1st day of admission before antibiotic usage.
- Two cultures (2%) of ceftriaxone receiving patients did isolate salmonella organisms even on 10th day of treatment.
- All culture sensitivities were sensitive to ceftriaxone, azithromycin & ciprofloxacin
- 1 culture organism had resistance to cotrimoxazole, two were resistant to ampicillin & three were resistant to chloramphenicol.

Comparative Outcome of The Study: (Table 2)

- It was observed that there was early clinical cure in cases treated with azithromycin than those with ceftriaxone, also was significant statistically (p=0.027). (Fig 1)
- The bacterial clearance in blood culture on 10th day was defined as microbiological cure, was not much differing in both study groups (p=0.131).

Clinical Features	Resolution of Symptoms and Signs							
	Day 1 N (%)		Day 3 N (%)		Day 5 N (%)		Day 7 N (%)	
	Azithromycin	Ceftriaxone	Azithromycin	Ceftriaxone	Azithromycin	Ceftriaxone	Azithromycin	Ceftriaxone
Fever	0 (0)	0 (0)	96 (96)	2 (4)	95 (95)	29 (29)	49 (98)	46 (92)
Abdominal pain	60 (60)	74 (74)	100 (100)	82 (82)	100 (100)	100 (100)	100 (100)	100 (100)
Constipation	100 (100)	45 (90)	100 (100)	98 (98)	100 (100)	100 (100)	100 (100)	100 (100)
Diarrhoea	78 (78)	42 (84)	100 (100)	90 (90)	100 (100)	100 (100)	100 (100)	100 (100)
Melena	100 (100)	49 (98)	100 (100)	100 (100)	100 (100)	100 (100)	100 (100)	100 (100)
Anorexia	68 (68)	32 (64)	96 (96)	76 (76)	96 (96)	90 (90)	100 (100)	98 (98)
Coated tongue	44 (44)	42 (42)	88 (88)	50 (50)	98 (98)	88 (88)	100 (100)	98 (98)
Abdominal tenderness	100 (100)	86 (86)	100 (100)	90 (90)	100 (100)	100 (100)	100 (100)	100 (100)
Hepatomegaly	54 (54)	57 (57)	82 (82)	54 (54)	98 (98)	84 (84)	100 (100)	94 (94)
Splenomegaly	28 (28)	48 (48)	70 (70)	48 (48)	98 (98)	80 (80)	100 (100)	98 (98)

Table 1. Comparison of Symptoms and Signs Between Azithromycin and Ceftriaxone Receiving Groups

Drug Susceptible	Percentage
Amoxycillin	100
Cefixime	100
Ceftriaxone	100
Azithromycin	90
Chloramphenicol	60
Cotrimoxazole	16
Ampicillin	50
Ciprofloxacin	78
Ofloxacin	85

Table 2. In Vitro Susceptibility/ Blood Culture Sensitivity of Salmonella Isolates from Culture Positive Subjects

Cure	Azithromycin Trial Group	Ceftriaxone Trial Group	p-Value
Clinical cure	98 (98%)	86 (86%)	0.027
Clinical failure	2 (2%)	14 (14%)	

Table 3. Clinical Outcome Comparison

DISCUSSION

This study compares the clinical & microbiological efficacy of oral Azithromycin with Intravenous ceftriaxone in treating children who had uncomplicated typhoid fever in age group

of 2 to 17 years, admitted Paediatric department of Dr. Prabhakar Kore Hospital & Research Unit of KAHER, attached to J N Medical College, Belagavi.

The two study groups were not differing in demographic data and chief complaints; were comparable. There was even distribution of severity of symptom in both the study groups, as even observed in other similar studies.^{7,8,9}

The 2 groups (Azithromycin and ceftriaxone receiving) were found comparable in all demographic data, presentation and were not significant statistically. Typhoid severity was equally distributed in both the groups. The complaint of fever in both treatment groups were in days (9-11 days) reported in prior published trials on the treatment of typhoid.^{7,8,9}

In present study, blood culture was done before first antibiotic dose after hospitalisation and second on 10th day of admission irrespective of the clinical outcome. Another similar study by Tribble D et. al., practiced blood culture sampling in between the study on 3rd and 7th day.

Our study has persistent bacteraemia (1 out of 5 culture positive) i.e., among ceftriaxone receiving patients 1 out of 5 cultures were still growing salmonella on 10th day of treatment. This finding is not similar to the study of typhoid fever using chloramphenicol and ceftriaxone comparatively, where 3rd day blood cultures for chloramphenicol receiving patients were still positive and those of ceftriaxone receiving patients were cleared (0 out of 28).¹⁰

Another very interesting finding we had was there was no correlation between in vitro resistance and in vivo effectiveness against Enteric fever. The possible reason being serum drug levels determine sensitivity/ susceptibility tests, but the main drug action of azithromycin is intracellular bactericidal action. Sometimes intracellular azithromycin levels increase to 100 times than of serum levels.^{11,12}

Similar study result was explained by Robert W Frenc k Jr et al. in a study.¹³

In our study we had documented a Relapse case who was treated with intravenous ceftriaxone. There were no relapses in azithromycin received group. The possible explanation for no relapses in azithromycin received patients is that, the azithromycin concentration being high intracellularly, its secretion in biliary tree and a relatively longer half-life.^{8,14,15}

Another similar trial conducted by Tribble D et.al., concluded that the high dose azithromycin for a short duration (20 mg/kg/day, maximum 1000 mg/day, for 5 days) is effective in treating enteric fever of uncomplicated type in children.^{13,15} A trial by Agarwal A et.al., in 2000 documented safe and effective therapeutic role of azithromycin (6days short course) in typhoid fever.¹⁶

In the current study a low dose Azithromycin is used for a short duration (10 mg/kg/day, OD, for 6 days) the reason being the possible adverse effects of high dose azithromycin. A study done by Saha S K et.al., used low dose azithromycin with no comparison with any other drugs; found to be effective in treating enteric fever in children.¹⁷

Based on parents' opinion, frequent need of intravascular access was a reason for non-compliance and oral once a day Azithromycin increased the compliance. Similar observations were quoted in studies of Robert W Frenck Jr et.al.^{13,12,17}

A much recent study from Vietnam reported that the decreased duration of azithromycin therapy can be equally effective in treating adult typhoid fever.¹⁷ This result encouraged us to use low dose, short duration Azithromycin in childhood enteric fevers.

Thus, our study clearly shows that the clinical cure is better in low dose, short duration oral Azithromycin regimen

than conventional intravenous ceftriaxone regimen; this observation was significant statistically ($p=0.026$). But the microbiological-cure was still comparable between two groups ($p=0.132$). Five more studies showed similarity in clinical and microbiological cures using oral Azithromycin and even there were microbiological-cure rates exceeding 90% without any significant adverse drug reactions or relapses in typhoid fever.^{7,15,16}

CONCLUSIONS

A short course of oral Azithromycin (10 mg/kg/day once a day for 6 days) is more efficacious in treating uncomplicated typhoid fever as compared to intravenous ceftriaxone (100 mg/kg/day in 2 DD for 7 days) in children and adolescents.

Study Limitations

1. In this study, we could not effectively describe the microbiological outcome, because blood culture yield was poor (only 12%), it is very much less than that described in the text books. Prior administration of antibiotics before admission to the study hospital was not addressed, which might have affected the culture results in the study.
2. Further multicentric trials with larger sample-size is recommended.

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REFERENCES

- [1] Byrne JP. Encyclopedia of pestilence, pandemics and plagues. Westport, Connecticut: Greenwood Press 2008;1(A-M):190.
- [2] USAMRMC: 50 years of dedication to the warfighter: 1958-2008. U.S. Army Medical Research and Material Command Headquarters, Government Publication 2008: p. 5.
- [3] Choo KE, Davies TME, Ismail A, et al. Rapid and reliable serological diagnosis of enteric fever: comparative sensitivity and specificity of Typhidot and Typhidot-M tests in febrile Malaysian children. Acta Tropica 1999;72(2):175-83.
- [4] Fuller GW. Description of the process and plant of the Jersey City water supply company for the sterilization of the water of the Boonton reservoir. Proceedings American Water Works Association 1909: p. 110-34.
- [5] Bhutta ZA. Salmonella. In: Behrman, Kliegman, Jenson, et al. eds. Nelson Text Book of Pediatrics. 18th edn. Philadelphia, PA: Elsevier/Saunders 2011: p. 1186-90.
- [6] Bhutta ZA, Mansurali N. Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: a prospective comparative evaluation of two dot-enzyme immunoassays and the Widal test. The

- American Journal of Tropical Medicine and Hygiene 1999;61(4):654-7.
- [7] Frenck RW Jr, Nakhla I, Sultan Y, et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis* 2000;31(5):1134-8.
- [8] Chinh NT, Parry CM, Ly NT, et al. A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. *Antimicrob Agents Chemother* 2000;44(7):1855-9.
- [9] Islam A, Butler T, Kabir I, et al. Treatment of typhoid fever with ceftriaxone for 5 days or chloramphenicol for 14 days: a randomized clinical trial. *Antimicrob Agents Chemother* 1993;37(8):1572-5.
- [10] Girgis NI, Butler T, Frenck RW, et al. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrob Agents Chemother* 1999;43(6):1441-4.
- [11] 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(2):243-50.
- [12] Rahman M. Treatment of enteric fever. *The ORION Med J* 2009;32(3):674.
- [13] Tribble D, Girgis N, Habib N, et al. Efficacy of azithromycin for typhoid fever. *Clin Infect Dis* 1995;21(4):1045-6.
- [14] Wildfeuer A, Laufen H, Zimmermann T. Distribution of orally administered azithromycin in various blood compartments. *Int J Clin Pharmacol Ther* 1994;32(7):356-60.
- [15] Rakita RM, Jacques-Palaz K, Murray BE. Intracellular activity of azithromycin against bacterial enteric pathogens. *Antimicrob Agents Chemotherapy* 1994;38(9):1915-21.
- [16] Aggarwal A, Ghosh A, Gomber S, et al. Efficacy and safety of azithromycin for uncomplicated typhoid fever: an open label non-comparative study. *Indian Pediatrics* 2011;48(7):553-6.
- [17] Saha SK, Talukder SY, Islam M, et al. A highly ceftriaxone resistant *Salmonella typhi* in Bangladesh. *Pediatric Infectious Disease Journal* 1999;18(4):387.