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Original Research Article

Azithromycin and ceftriaxone in uncomplicated typhoid fever in paediatric patients: a prospective, comparative and randomized open labelled trail

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ABSTRACT

Background: Typhoid fever is a life-threatening infection caused by the bacterium *Salmonella typhi*. There are limited options for treatment of typhoid fever in children. Carbapenems and azithromycin are two drugs which is available for treatment of infection caused by extensively drug-resistant (XDR) strain of *Salmonella typhi*.
Methods: This is a prospective, comparative, randomized open labelled trail conducted in the department of paediatrics Konaseema institute of medical science, Amalapuram, Andhra Pradesh. Blood sample was obtained from each patient before start of treatment for determination of complete blood count and differential count at baseline. Everyday each patient was evaluated clinically.
Results: The mean duration of fever after start of treatment was 4.41.46 days in group treated by azithromycin and 3.95+1.02 days in group treated by ceftriaxone which is little early without statistical significance.
Conclusions: From present study we can conclude that azithromycin 20 mg/kg/day is as effective as ceftriaxone 75 mg/kg/day for the treatment of typhoid fever in children. Clinical and microbiological cure was comparable in both groups. There was no incidence of relapse of fever in azithromycin treatment group. Diarrhoea was common in patients treated with ceftriaxone and nausea and vomiting was more common in patient treated with azithromycin.

Keywords: Typhoid fever, Azithromycin, Ceftriaxone

INTRODUCTION

Typhoid fever is a life-threatening infection caused by the bacterium *Salmonella typhi*. It is a systemic infection characterized by prolonged fever, loss of appetite, nausea, and headache. It is an infectious disease transmitted through contamination of food or water. An estimated 11-20 million people get sick from typhoid and between 128 000 and 161 000 people die from it every year.[1] Typhoid fever can be treated with antibiotic. Chloramphenicol was first used in the treatment of typhoid in 1948 by Woodward and many patients were treated successfully but in 1970 salmonella became resistant to it.[2] In late 1980 and early 1990 salmonella became resistant to cotrimoxazole and ampicillin also and became multidrug resistance typhoid fever. When salmonella typhi are resistant to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole they are called multidrug-resistant typhoid fever (MDRTF).[3] Fluoroquinolones have proven to be effective but they are restricted from routine use in children, and quinolone-resistant strains of *Salmonella typhi* have begun to be reported.[4] Now XDR strain of *Salmonella typhi* has been reported which is resistant to most antibiotics (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, ciprofloxacin, and

ceftriaxone) used to treat typhoid fever. There are limited options for treatment of typhoid fever in children. Carbapenems and azithromycin are two drugs which is available for treatment of infection caused by XDR strain of *Salmonella typhi*.

Various studies are available regarding efficacy of azithromycin for treatment of typhoid fever in comparison to ceftriaxone. Frenck et al from USA has concluded in his study that oral azithromycin administered once daily appears to be effective for the treatment of uncomplicated typhoid fever in children.[5] Nair et al from New Delhi has concluded that oral azithromycin could be a convenient and cheap alternative for the treatment of typhoid fever, especially in children in developing countries. Aggarwal et al has concluded in his study that azithromycin was found to be safe and efficacious for the management of uncomplicated typhoid fever.[7]

These results have encouraged us to compare clinically efficacy oral azithromycin verses intravenous ceftriaxone for treatment of uncomplicated typhoid fever in paediatric patients.

METHODS

This is a prospective, comparative, randomized open labelled trail conducted in the department of paediatrics Konaseema institute of medical science Amalapuram, Andhra Pradesh from January 2018 to June 2020.

Ethics

Approval from institutional ethics committee was taken before start of study. A written informed consent was obtained from all patients before enrolling them for study.

Selection of patients

Paediatric with fever admitted in the department of paediatric and also those with fever for evaluation with WIDAL positive (TO titre equal or >1:160 with TO>TH) were included in this study based on following inclusion and exclusion criteria.

Inclusion criteria

The student included participants between the age group 2 to 18 years of both sexes; and patients with fever since 4 days with additional clinical features like splenomegaly, hepatomegaly, abdominal tenderness, and/or a coated tongue.

WIDAL test positive was done in 2nd week of fever with TO titre equal or >1:160.

Exclusion criteria

Patients who were treated with antimicrobial agents after fever, patients with typhoid fever with complications, hypersensitivity to drug used and patients with inability to swallow oral medications were excluded from the study.

Sample size

Based on inclusion and exclusion criteria 100 patients were enrolled for this study. Each patient was randomly assigned in to two treatment groups. Group A consist of 50 patients treated with azithromycin 20 mg/kg/day; and group C consist of 50 patients treated with ceftriaxone 75 mg/kg/day. For assignment of treatment we use block randomization method. Subjects and investigators were blinded about treatment before randomization after that patients were treated in an open level format.

Method

After enrolment of patient demographic details of the patient, presenting complaints, symptoms, Widal test report, and temperature were recorded in predesigned performa.

Blood sample was obtained from each patient before start of treatment for determination of complete blood count and differential count at baseline. Everyday each patient was evaluated clinically. Various parameters like temp, headache, appetite, hepatosplenomegaly, constipation or diarrhoea, and abdominal pain were recorded. By using standard clinical methods Blood culture is done on day 1 and day 10 to correlate the treatment efficacy- clinically and microbiologically. Patients were monitored for side effect of drug used.

We defined clinical cure as resolution of signs and symptoms by the end of 7 days of treatment, defervescence was defined as body temperature below 37 ^{0}C for 72 hours. Microbiological cure was defined as sterile blood culture after 10th day of treatment and failure if it is positive after 10th day of treatment. Persistence of symptom after 5th day of treatment was defined as clinical failure and recurrence of fever after 4 weeks with positive culture was defined as replace of typhoid fever.

Statistical analysis

Data were recorded in excel sheet and statistical analysis was done with software statistical package for social sciences (SPSS)-14 version. Qualitative data were calculated as percentage and proportions and were analyzed by Chi-square test. Quantitative data were expressed as mean±standard deviation (SD) and these data were analyzed by unpaired student t test. The p value less than 0.05 were taken as significant.

RESULTS

In this open level randomized trial 100 patients were enrolled as per inclusion and exclusion criteria. Each patient was randomly assigned in to two treatment groups. Both groups were comparable to each other with respect to

age and sex. Mean age of patients in group A was 9.64±3.57 years and group C was 9.96±3.32 years. The difference was not significant statistically (p=0.35). The mean duration of fever in group A was 9.73±1.96 days and in group C was 10.3±1.80 days. Both groups were comparable to each other with respect to duration of fever before treatment.

Regarding clinical, haematological and biochemical parameters at admission 56% patients have diarrhoea in group A and 44% in group C. Vomiting was present in 16% patient in group A and 12% in group C. Pain abdomen was present in 12% patient in group A and 10% in group C. Both groups were comparable to each other with respect to haemoglobin concentration, white blood cells (WBC) and platelet count (p value was more than 0.05). All these parameters were in normal range. Hepatic and renal parameters were also in normal range and comparable to each other statistically (p value was more than 0.05).

The mean duration of fever after start of treatment was 4.4±1.46 days in group treated by azithromycin and 3.95±1.02 days in group treated by ceftriaxone which is little early without statistical significance. Clinical and microbiological cure was marginally higher in group A than group C. Only one patient blood culture was positive after 3 days and 7 days of treatment. There was no recurrence in group A but one patient in group C has recurrence of fever. Both groups were comparable to each other with respect to haemoglobin concentration, WBC and platelet count after 7 days of treatment (p value was more than 0.05). All these parameters were in normal range. Hepatic and renal parameters were also in normal range and comparable to each other statistically after 7 days of treatment (p value was more than 0.05).

Table 1: Demography of patients in two groups.

Variables		Group A	Group C	P value
Age (mean±SD)		9.64±3.57	9.96±3.32	0.35
Sex	Male	28	26	0.60
	Female	22	24	
Duration of fever (mean±SD)		9.73±1.96	10.3±1.80	0.12

Table 2: Clinical, haematological and biochemical parameters at admission.

Variables	Group A (%)	Group C (%)	P value
Diarrhoea	28 (56)	22 (44)	
Vomiting	8 (16)	6 (12)	
Pain abdomen	12 (24)	10 (20)	
TWBC (10^3 cell/mm^3) (mean±SD)	6.31±0.95	5.9±1.0	0.14
Hb mg/dl (mean±SD)	11.51±1.6	11.05±2.04	0.25
Platelet count (10^5 cell/mm^3) (mean±SD)	2.47±0.52	2.61±0.36	0.08
AST (IU/L) (mean±SD)	45.6±17.3	43.25±9.99	0.40
ALT (IU/L) (mean±SD)	42.8±9.43	40.3±7.55	0.19
Total bilirubin mg/dl (mean±SD)	0.62±0.23	0.54±0.86	0.09
Blood urea mg/dl (mean±SD)	18.24±0.47	15.64±0.76	0.12
Serum creatinine mg/dl (mean±SD)	0.76±0.54	0.84±0.39	0.63

Table 3: Clinical, haematological and biochemical parameters after 7 days.

Variables	Group A	Group C	P value
Duration of fever after start of treatment (mean±SD)	4.4±1.46	3.95±1.02	1.39
Clinical cure after 7 days (%)	48/50 (96)	47/50 (94)	
Clinical cure after 30 days (%)	50/50 (100)	50/50 (100)	
Microbiological cure after 7 days (%)	49/50 (98)	48/50 (96)	
Positive blood culture after 3 days	1	1	
Positive blood culture after 7 days	1	1	
Recurrence of fever	0	1	
TWBC (mean±SD)	5.91±0.68	6.24±0.65	0.09
Hb% (mean±SD)	12.21±1.6	10.25±1.94	0.29
Platelet count (mean±SD)	2.47±0.52	2.61±0.36	0.08
AST (mean±SD)	45.6±17.3	43.25±9.99	0.40
ALT (mean±SD)	39.58±8.99	41.8±7.55	0.09

Continued.

Variables	Group A	Group C	P value
Total bilirubin (mean±SD)	0.70±0.36	0.68±0.49	0.26
Blood urea (mean±SD)	20.32±0.47	18.94±0.67	0.38
Serum creatinine (mean±SD)	0.89±0.19	0.90±0.24	0.43

There was no serious adverse drug reaction in both groups. Gastrointestinal symptom was more common both group. Diarrhoea was more common in ceftriaxone group and anorexia was more common in ceftriaxone group.

Table 4: Adverse drug reaction.

Variables	Group A	Group C
Diarrhoea	5	7
Pain abdomen	4	3
Nausea and vomiting	8	6
Skin rashes	4	2
Anorexia	6	3

DISCUSSION

Even after availability of effective anti-microbial agent, treatment of typhoid fever in children is still a challenge. Wain et al in his article published in The Lancet 2015 has mentioned that non immunogenicity of vaccine in children and development of multidrug-resistant (MDR) and XDR strain of Salmonella typhi are main barriers to control typhoid fever in children.[8] In present comparative, randomized open labelled trail we have evaluated two drugs azithromycin and ceftriaxone for the treatment of uncomplicated typhoid fever in children. Patients enrolled in this study were divided in to two groups. Group A consist of 50 patients treated with azithromycin (20 mg/kg/day) and group C consist of 50 patients treated with ceftriaxone (75 mg/kg/day). Both group were comparable to each other statistically with respect to age (9.64±3.57 years versus 9.96±3.32 years), sex and duration of fever (9.73±1.96 versus days 10.3±1.80). This corroborates with the study of Frenck et al and Mansour et al.[5,9] Both groups are comparable to each other with regard to clinical, biochemical and haematological parameters before start of treatment). This finding is supported by the work of Nair et al and Girgis et al.[6,10]

Duration of fever after start of treatment was comparable to each other in both treatment groups (4.4±1.46 days versus 3.95±1.02 days). This finding corroborates with the study of Chandey et al and Smith et al.[11,12] In present study there is 96% cure rate with azithromycin and 94% with ceftriaxone after 7 days and 100% in both group after 30 days. This finding is supported by the work of Tribble et al, Wallace et al and Frenck et al.[5,13,14] In present study there is 98% microbiological cure rate with azithromycin and 96% with ceftriaxone after 7 days. There is no recurrence of fever in azithromycin group. Study of Nair et al and Simalti et al.[6,15] There is no statistically significant difference between biochemical and haematological parameter between two groups which is similar to the work of Frenck et al.[5]

In our study we have not observed any serious adverse drug reaction. Gastrointestinal adverse effect was common in both groups. Nausea and vomiting was common in azithromycin and diarrhoea was common in ceftriaxone group. This finding is supported by the meta-analysis of Trivedi et al.[16]

CONCLUSION

From present study we can conclude that azithromycin 20 mg/kg/day is as effective as ceftriaxone 75 mg/kg/day for the treatment of typhoid fever in children. Clinical and microbiological cure was comparable in both groups. There was no incidence of relapse of fever in azithromycin treatment group. Diarrhoea was common in patients treated with ceftriaxone and nausea and vomiting was more common in patient treated with azithromycin.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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