Section A-Research paper
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Comparison of Ceftriaxone Versus Ceftriaxone- Azithromycin Combination in the Treatment of Culture Positive Cases of Enteric Fever

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Abstract

Introduction: Typhoid is the most prevalent bacterial cause of fever among migrants and visitors who have just left these regions. According to estimates from the Global Burden of Disease Study in 2017, 136 000 fatalities occur yearly, mostly in low- and middle-income countries, and there are around 14 million afflicted individuals.

Objective: To compare the time of defervescence with Ceftriaxone and Ceftriaxone-Azithromycin combination in all cases of culture proven Enteric fever (typhoid/paratyphoid) and to assess the improvement of general wellbeing and hepatosplenomegaly.

Material and Methods: This was a randomized controlled clinical trial conducted among 38 children between the ages of 1year to 18 years with culture positive enteric fever treated at the hospital. All the cases with blood culture positive for enteric fever i.e., S. Typhi and S. Paratyphi A and B grown on culture were divided into two groups. The first group was given IV Ceftriaxone at a dose of 100 mg/kilogram of bodyweight/day along with antipyretics. The second group was given IV Ceftriaxone at a dose of 100mg/kilogram bodyweight/day and Oral Azithromycin at a dose of 10mg/kilogram bodyweight/day as once a day dosing.

Results: In the study mean day of fever Defervescence was 5.63 ± 1.89 days in group 1 and 3.89 ± 1.15 days in group 2. This difference in mean Day of Defervescence of fever between two groups was statistically significant. i.e., in Group 2 fever was reduced within 4 days. (p=0.002). All the subjects in both the groups had improvement. In our study, no case of relapse was found in both the groups when followed up over four weeks. In Ceftriaxone group among 17 subjects with Hepatomegaly and 13 subjects with splenomegaly all the subjects showed reduction in size at discharge and similarly in ceftriaxone + Azithromycin all the 18 subjects with hepatomegaly and 5 subjects with splenomegaly showed reduction in size at discharge.

Conclusion: It is hypothesized that combination treatment might prevent the emergence of multidrug resistance in S. Typhi.

Keywords: Typhoid, Ceftriaxone, Azithromycin, Blood culture.

Introduction

World-wide an estimated 17 million cases of enteric fever and 6,00,000 associated deaths occur annually[1]. Enteric fever remains one of the most prevalent infections in developing countries like India. It is a disease of poor environmental sanitation and hence occurs in parts

of the world where water supply is unsafe and sanitation is substandard. Typhoid fever was first described by Thomas Willis in 1659[2]. William Wood Gerhard was the first to differentiate clearly between typhus fever from typhoid in 1837[3]. Budd in 1856 pointed out that the disease was transmitted through the excreta of patients[4]. The Typhoid bacillus was discovered by Carl Joseph Eberth in 1880[5].

Its causative role was confirmed by Metchnikoff and Besredka by infecting apes experimentally in 1900[6]. Enteric fever includes Typhoid fever caused by *Salmonella enterica* serovar Typhi and Paratyphoid fever caused by *Salmonella enterica* serovar Paratyphi *A*, *B*, or *C* [7]. These organisms cause disease specifically in humans.

History, physical findings and fever pattern though suggestive can neither confirm nor exclude enteric fever. Blood culture is the gold standard for diagnosis of enteric fever[8]. But non-availability and poor affordability by parents are practical hurdles encountered in clinical practice. Hence many clinicians rely on use of Complete blood count and Widal test for suspecting or excluding diagnosis of enteric fever. But Complete blood counts and Widal test are neither sensitive nor specific.

Blood culture is 100% specific, gives information on antimicrobial susceptibility of the isolate, is cost effective in the long run and is particularly important as other diagnostic methods are suboptimal[9]. Towards the end of the 1980s and in the early 1990s, S.Typhi developed plasmid-mediated resistance simultaneously to all the drugs that were then used as first line treatment (Chloramphenicol, Trimethoprim, Sulfamethoxazole and Ampicillin)[10]. However, concerns of toxicity have precluded their widespread use and beta lactams such as Ceftriaxone and Cefixime are now used as first line agents for therapy of enteric fever.

The objective of present study is to compare the time of defervescence with Ceftriaxone and Ceftriaxone-Azithromycin combination in all cases of culture proven Enteric fever (typhoid/paratyphoid) and to assess the improvement of general wellbeing and hepatosplenomegaly.

Material and Methods

Study design: Present study was a randomized controlled clinical trial conducted at the Department of Pediatrics, Church of South India Hospital, a tertiary care hospital in Bangalore for a period of 1 year. Children between the ages of 1year to 18 years with culture positive enteric fever treated at the hospital. An informed written consent was taken by the parents for inclusion of their child in this study.

Sample size estimation: As there were no previous literature available on the enteric fever comparing both the drugs, a Pilot study was done to obtain the mean day of Defervescence of fever. And sample size was estimated by using the values obtained from the pilot study. Mean day of defervescence of fever in ceftriaxone group was 5.2 ± 1.6 days and in Ceftriaxone + Azithromycin group was 3.6 ± 1.1 days. With these values at 95% Confidence limit and 90% power sample size of 16 was obtained in each group. With 10% nonresponse sample size of 17 + 1.7 ≈ 19 cases were to be included in each group. 38 cases were randomized in to two groups. Sample size was estimated by OPEN EPI software.

Inclusion and exclusion criteria: All children aged 1year to 18 years presenting with symptoms such as prolonged fever (fever for 5 or more days), fever is defined by an axillary

temperature greater than 100-degree Fahrenheit, recorded by digital thermometer with variation of $\pm 1^0$F, malaise anorexia, disturbances of bowel (constipation/diarrhoea) and consented by parents or care givers are included in the study. Any child presenting with fever and definite evidence of involvement of other organs systems [like respiratory tract, urinary tract, etc.] are excluded from study. Drop outs are excluded from study.

Sampling technique: 38 children were randomly allocated to two groups in the ratio of 1:1 by block randomization; randomization code being obtained from www.randomization.com

Interventions: All the patients who fulfilled the inclusion criteria were enrolled in the study after written parental consent. Detailed history was taken. They underwent a thorough physical examination, assessment of vital signs, systemic examination. Blood was collected for Complete blood count, typhidot, widal test and blood culture as per standard protocols.

Blood culture bottle is inserted into BACTEC and run. If there is growth in the culture bottle, machine shows red signal in the respective position. The bottle is then taken out and cultured on MacConkey, Blood and chocolate agars and simultaneously smears made from the same. Culture plates are read after 24 hours. If there is no growth, blood is further sub cultured and run in BACTEC for 5 days. WIDAL test is done as per the standard protocols and S. typhi O Ab and S. typhi H Ab titres of 1:160 and S. paratyphi AH Ag, S. paratyphi BH Ag titres of 1:80 is considered positive

All the cases with blood culture positive for enteric fever i.e., S. Typhi and S. Paratyphi A and B grown on culture were divided into two groups. The first group was given IV Ceftriaxone at a dose of 100 mg/kilogram of bodyweight/day along with anti pyretics. IV Ceftriaxone was given for a duration of 10 days. The second group was given IV Ceftriaxone at a dose of 100mg/kilogram bodyweight/day and Oral Azithromycin at a dose of 10mg/kilogram bodyweight/day as once a day dosing[83]. IV ceftriaxone was given for 10days and oral azithromycin for 7days.

Statistical Analysis: Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Bar diagram and pie charts were plotted to show the data graphically. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two groups. p value <0.05 was considered as statistically significant.

Results

In the study 38 subjects with Enteric Fever (all subjects Culture positive for S. Typhi and S. Paratyphi) were included and 19 subjects received Ceftriaxone and 19 subjects received Ceftriaxone + Azithromycin. In the study majority of subjects in both groups were males. 78.9% in Group 1 and 57.9% in Group 2 were Males. However, there was no statistically significant difference in gender between the two groups (p=0.163). In Group 1 Mean weight was 27.27 ± 16.05 Kgs, mean height was 126.79 ± 31.67 cms and Mean BMI was 15.59 ± 3.43. In group 2 Mean weight was 37.84 ± 16.36 Kgs, mean height was 142.16 ± 27.4 cms and Mean BMI was 17.7 ± 3.01. There was no significant difference in Mean Weight, Height and BMI between both groups.

Variable		Ceftriaxone		Ceftriaxone + Azithromycin		P value
		Count	%	Count	%	
Pattern of fever	Continuous	1	5.3%	3	15.8%	0.290
	Intermittent	18	94.7%	16	84.2%	
Headache	No	15	78.9%	10	52.6%	0.087
	Yes	4	21.1%	9	47.4%	
Malaise	No	12	63.2%	8	42.1%	0.194
	Yes	7	36.8%	11	57.9%	
Anorexia	No	19	100.0%	18	94.7%	0.311
	Yes	0	0.0%	1	5.3%	
Vomiting	No	7	36.8%	7	36.8%	1.000
	Yes	12	63.2%	12	63.2%	
Abdominal discomfort	No	10	52.6%	11	57.9%	0.744
	Yes	9	47.4%	8	42.1%	
Diarrhoea	No	15	78.9%	17	89.5%	0.374
	Yes	4	21.1%	2	10.5%	
Constipation	No	19	100.0%	18	94.7%	0.311
	Yes	0	0.0%	1	5.3%	

Table 1: Clinical Presentation of subjects.

In Group 1 mean temperature was 102.11 ± 1.73 ° F and in Group 2 Mean temperature was 102 ± 1.2 ° F, there was no difference between two groups(p=0.829). Similarly, the duration of fever before hospitalisation was 6.95 days in group 1and 7.32 days in group 2. There was no statistically significant difference between two groups. (p=0.772). In Group 1, 5.3% was vaccinated for Typhoid and 36.8% had history of prior antibiotic use. Were as in Group 2 none of them were vaccinated for typhoid and 31.6% had history of prior antibiotic use. There was no statistically significant difference between two groups. In the study Mean PR in group 1 was 107.37 ± 10.35 bpm and in group 2 mean PR was 104.11 ± 6.09 bpm. Mean RR in group 1 was 20.21 ± 3.39 bpm and in group 2 mean RR was 19.00 ± 1.91. There was no significant difference between two groups.

In Group 1 5.3% had Pallor, 89.5% had Hepatomegaly and 68.4% had Splenomegaly. In Group 2 5.3% had pallor, 94.7% had Hepatomegaly and 26.3% had splenomegaly. There were no other signs such as icterus, cyanosis, clubbing, lymphadenopathy and edema in both the groups. There was no significant difference in clinical signs between two groups except for Splenomegaly. Group 1 had higher percentage of splenomegaly than in group 2 which was statistically significant (p=0.009).

Variable	Ceftriaxone		Ceftriaxone + Azithromycin		Total		P value
	Mean	SD	Mean	SD	Mean	SD	
Hb (gms)	11.89	1.15	12.00	1.37	11.95	1.25	0.799
TC	6658.95	2730.61	5978.95	1715.15	6318.95	2275.35	0.364
Neutrophils	68.05	7.37	67.16	8.71	67.61	7.97	0.734
Eosinophils	1.68	0.75	2.11	0.88	1.89	0.83	0.120

Basophils	11.05	1.68	10.63	1.30	10.84	1.50	0.394
Monocytes	18.95	1.68	17.68	2.52	18.32	2.21	0.077
ESR	38.16	15.65	37.11	15.75	37.63	15.50	0.837

Table 2: Complete blood profile of the study participants.

In the study mean day of fever Defervescence was 5.63 ± 1.89 days in group 1 and 3.89 ± 1.15 days in group 2. This difference in mean Day of Defervescence of fever between two groups was statistically significant. i.e., in Group 2 fever was reduced within 4 days. (p=0.002).

Variable		**Ceftriaxone**		**Ceftriaxone + Azithromycin**		**P value**
		Count	**%**	**Count**	**%**	
Widal titer	Negative	6	37.50	6	35.29%	
Widal titer	Positive	10	62.50	11	64.70%	1.000

Table 3: WIDAL test results in the study participants.

Variable		**Ceftriaxone**		**Ceftriaxone + Azithromycin**		**P value**
		Count	**%**	**Count**	**%**	
Organism	S. typhi	15	78.9%	17	89.5%	
	S. paratyphi A	4	21.1%	2	10.5%	0.374

Table 4: Organism isolated in the culture in study subjects.

All the subjects in both the groups had improvement. In our study, no case of relapse was found in both the groups when followed up over four weeks. In Ceftriaxone group among 17 subjects with Hepatomegaly and 13 subjects with splenomegaly all the subjects showed reduction in size at discharge and similarly in ceftriaxone + Azithromycin all the 18 subjects with hepatomegaly and 5 subjects with splenomegaly showed reduction in size at discharge.

Discussion

Enteric fever continues to remain a health problem as the causative organisms have developed resistance to many of the antibiotics used**.** By the end of 1990s, Salmonella enterica developed resistance simultaneously to all first line drugs namely chloramphenicol, cotrimoxazole and ampicillin. Fluoroquinolones when first introduced in early 1990's were very effective but the past decade has seen a progressive increase in the MICs of ciprofloxacin and high incidence of clinical failure to quinolones[11].

There have also been sporadic reports of high-level resistance to ceftriaxone in S. typhi and S. paratyphi[12]. Experience with new drugs such as azithromycin is at present scanty. This randomized controlled trial aims to study and compare the efficacy of Ceftriaxone alone vs combination treatment with Azithromycin and Ceftriaxone in the treatment of Enteric Fever in children.

The primary outcome measure was the time of defervescence. Our study shows that there was a significant difference in the time of defervescence between the two groups. The difference in mean time of defervescence between the Ceftriaxone group and Ceftriaxone and Azithromycin combination group was 2days.

This is in contrast with the results of study done by J. Gavhane Et.al[13]. Their study showed that there was no difference in mean time to defervescence with combination therapy which included Ceftriaxone and Azithromycin. However, the dose and duration of Azithromycin used in their study has not been mentioned.

In a study by Frenck W Robert Et.al[14] where they have compared IV Ceftriaxone and Oral Azithromycin given alone, they have found that there was no significant difference between the time of defervescence between the two groups and concluded that 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 treatment of uncomplicated typhoid fever in children, with clinical cure rates comparable to those for ceftriaxone.

The Cost of treatment with Ceftriaxone-Azithromycin was compared with that of Ceftriaxone alone. A child weighing 20 kg would require a total of 35 ml of Azithromycin 200 mg/5 ml. This costs Rs.120.00. But since the defervescence of fever occurs 2 days earlier in this group the duration of hospitalization can be reduced by two days which works out to a reduction of the Hospital Bill by at least Rs.1000.00 in a general ward. This savings is in addition to the indirect costs like cost of travel and food for the parents of the child.

There was no increase in the drug related adverse events in Group 2 compared to that in Group 1 proving that the combination of Ceftriaxone and Azithromycin is safe and well tolerated by the patients. The other factor conducive to superiority in our study is Once-a-day dosing of Azithromycin which improves the compliance and because of early defervescence, DALY (Disability adjusted life year) can be reduced.

It is hypothesized that combination treatment might prevent the emergence of multidrug resistance in S. Typhi as proved in case of Tuberculosis and Malaria. No relapses were found in both the groups when followed over a period of four weeks. Our study had a few limitations. As only culture positive enteric fever cases were included, those with clinically diagnosed to have enteric fever but culture negative due to prior usage of antibiotics were excluded.

Conclusion

Azithromycin-Ceftriaxone combination can be given to all children with Enteric fever. The Azithromycin-Ceftriaxone combination could be given for 7 days instead of the present practice of giving Ceftriaxone for 10 days. The total duration of hospitalization can then be reduced as it is cost effective to give Azithromycin and Ceftriaxone for 7days and follow it up with 7 days of oral Cefixime at home as described earlier. However, further studies are required to conclusively establish the duration of Ceftriaxone treatment when given along with Azithromycin. It is hypothesized that combination treatment might prevent the emergence of multidrug resistance in S. Typhi. Further studies are recommended to prove this hypothesis. Typhoid vaccine is recommended to all children since most of the subjects in the present study were unimmunized against typhoid. Blood cultures are recommended in all cases who are clinically suspected to have Enteric Fever wherever feasible. Delaying the collection of blood for culture by 24 hours in patients who are on prior antibiotic therapy may increase the yield of positive blood culture.

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