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Clinical Outcome of Single Antibiotic versus Combination Antibiotics in Enteric Fever

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Abstract

Background: In recent times the treatment of enteric fever is becoming more and more difficult. The aim of our study was to find out a cost-effective way of treatment of enteric fever and to determine the success rate & fever clearance time of ceftriaxone as monotherapy in comparison to combinations of cefixime plus azithromycin. **Methods:** Randomized single-blind controlled comparative experimental study carried at the department of Medicine in Sheikh Hasina Medical College and Hospital, Jamalpur, Bangladesh during the period from August 2017 to April 2018. A total of 100 cases of enteric fever patients were included based on inclusion and exclusion criteria. After taking informed written consent data was collected by a questionnaire and relevant investigations were done. The Control group was given inj. ceftriaxone and the experimental group were given cefixime plus azithromycin. Then collected data was analyzed. Main Outcome measures: Age, Sex, response to treatment of Fever, Myalgia, Headache, Anorexia, Constipation, Diarrhoea, Abdominal pain, Cough, Relative bradycardia, Rose spot on the trunk, Splenomegaly, Hepatomegaly, Coated tongue, and treatment failure. **Results:** Out of 100 cases the majority of cases were seen in the age group of 18-25 years (30%), followed by 26-33 years (24%). There was a slight male preponderance with 53% male and 47 % female. A majority (48%) of cases were brought to the hospital during the 1st week of illness. Fever was common in all of the cases, followed by headache (63%), anorexia, and nausea (62%), abdominal pain (58%), diarrhea (52%), constipation (29%), and vomiting (8%). Less common symptoms were cough (15%), generalized weakness (8%), jaundice (4%), and bloody diarrhea (2%). None of the patients had G.I bleeding or rash. Coated tongue was present in 83% of patients. Hepatomegaly was present in 67% of patients and more common than splenomegaly (42%). Only 42% of patients were toxic-looking. Abdominal tenderness was present in 25% of patients, while abdominal distention in 19%. Caecal gurgling and relative bradycardia in 10% each. The mean period of defervescence was 5.4±1.09 days for the Ceftriaxone group and 4.2+ 0.91 days for Cefixime plus Azithromycin group, which is statistically significant. ($p = .04$). Duration of therapy was 9.92+ 4 days in group A and 7+ 0.00 days in group B, this is statistically significant. ($p < 0.001$). Out of 50 cases in group A, 45 patients become afebrile with ceftriaxone treatment, the success rate was 90%. Out of 50 cases of group B, 2 patients failed to respond and the success rate is 96%, but this is not statistically significant ($p = 0.399$).**Conclusion:** The treatment of enteric fever with a combination of antibiotics like Cefixime plus Azithromycin is not inferior to a single antibiotic like Ceftriaxone but oral combinations of antibiotics provide a less costly and equally safe and effective oral form of treatment alternative to ceftriaxone. Findings of this were also in accordance with the previous studies with enteric fever. As a small number of patients were studied so findings of this study should be cautiously extrapolated into the broader context.

Keywords: Enteric Fever, Antibiotic, Ceftriaxone, Cefixime, Azithromycin.

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INTRODUCTION

Despite advances in technology and public health strategies, enteric fever, more commonly known as typhoid fever, remains a major cause of morbidity & mortality in the developing world. It is a potentially fatal multisystemic illness, primarily caused by Salmonella Typhi and to a lesser extent, S enterica serotypes paratyphi A, B, and C. Worldwide, 22 million infections occur with this organism annually, resulting in almost 200,000 deaths.[1] The highest incidence of the disease is prevalent in the Indian subcontinent, which is an epicenter of enteric fever caused by multidrug-resistant (MDR and nalidixic acid-resistant (NAR) strains, i.e., strains with decreased susceptibility to ciprofloxacin.[2-4]

A total of 57% of S. Typhi strains isolated at a referral center in Dhaka, Bangladesh, in 2005 were MDR and NAR.[5] The emergence of multidrug-resistant (MDR) S. Typhi led to the introduction of fluoroquinolones as the first-line drug during the last two decades of the 20th century.[6] However, frequent treatment failures of ciprofloxacin against S. Typhi have resulted in the use of third-generation cephalosporins for fluoroquinolones-resistant Salmonella infections. Coincidently, ceftriaxone-resistant S. Typhi has already been reported from Asia.[7]

Some patients with enteric fever can show a delayed response or treatment failure with ciprofloxacin both clinically and bacteriologically.[8] No optimum treatment for MDR and NAR enteric fever has been established yet. A third-generation cephalosporin or high doses of fluoroquinolones (e.g., ciprofloxacin, 20 mg/kg/day or levofloxacin, 10 mg/kg/day) for 10–14 days are the drugs of choice.[2,3] Azithromycin (20mg/kg/day) is also a promising agent.[9] However, for any of the mentioned regimens, the mean fever clearance times are relatively long (≈7 days), and the relapse rates are high.[2] So a combination of these regimens can be considered.[10] Towards the end of the last decade, it was observed that fever took a longer time than before to clear, and at times failed to respond to ciprofloxacin therapy resulting in a significant reduction of workload.[11-13] However, it is not clear whether fluoroquinolones can still be used as a first-line drug for the treatment of enteric fever. Ceftriaxone, a 3rdgeneration cephalosporin has become the treatment of choice for typhoid fever in many parts of the world. But the recent report of an isolate of Salmonella Typhi from Bangladesh with a high level of resistance to ceftriaxone means that untreatable enteric fever is a real problem.[14] Because of its high cost, parenteral administration, and requiring hospitalization, ceftriaxone is less than an ideal treatment option in a low resource country like ours. The availability of the Macrolide class of antibiotics has provided another potential option for the treatment of enteric fever.[15] Rapid movement of azithromycin from the blood into tissues results in significantly higher

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concentration in tissue than in plasma. The serum concentration of azithromycin declines in a polyphasic pattern, resulting in an average half-life of 68 hours,[16] the prolonged concentration of azithromycin in cells may explain the better results obtained with azithromycin in patients from other studies conducted overseas.[17,18] Cefixime, an orally administered third-generation cephalosporin, is a commonly used drug in South Asia for the treatment of enteric fever. Although cefixime is recommended as a drug of choice by the World Health Organization (WHO) for the treatment of resistant typhoid fever it needs to be administered for a longer duration than the currently used fluoroquinolones.[19] Cefixime is widely trusted to be effective for enteric fever as the first line of treatment and is also used as a second-line therapy when initial treatment with a fluoroquinolone in a patient suspected to be enteric fever fails.[20] The mechanism of action of cefixime was found to be behind the high overall failure rate associated with cefixime despite all of the strains being fully sensitive in vitro to the drugs.[21,22] As such, this may not be suited to the eradication of S. Typhi or Paratyphi A from the body or blood, and the poor intracellular penetration into macrophages and reticuloendothelial tissues where the typhoid organisms colonize may be the cause of high failure rates.[23] This shows the urgent need for a treatment that combines ease of oral administration,[24] with the speed of clinical response, reduction in secondary transmission, and inexpensiveness. So the encouraging results of azithromycin and trusted oral third-generation cephalosporin, cefixime combination may help us to choose a safer, cheap, and effective alternative to other available drugs. In this scenario, the present study is undertaken to compare the efficacy of ceftriaxone Vs cefixime plus azithromycin in enteric fever to reduce the cost of treatment to approximately 80%, need for hospitalization, reduce the bed occupancy rate and hazards of intravenous administration.

The treatment of enteric fever is becoming more and more difficult in recent times. In spite of the use of different antibiotics delayed clinical response is a common scenario. So further research work especially in Bangladesh may be helpful considering the demographics, widespread irrational use of antibiotics, and prevailing antibiotic resistance pattern.

MATERIALS AND METHODS

It was a randomized single-blind controlled comparative experimental study carried at the department of Medicine in Sheikh Hasina Medical College and Hospital, Jamalpur, Bangladesh during the period from August 2017 to April 2018. One hundred (100) patients with enteric fever were purposively selected for the study. All culture-proven cases of Enteric fever. After registration of the patient, detailed history was taken and a physical examination was done. Samples of blood were collected for complete blood count, comment on peripheral blood film with a malarial

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parasite, blood culture & sensitivity, and a Widal test. After completion of treatment with clinical cure enrolled patients were discharged. All subjects in both the group were asked to return immediately if fever develops within four weeks after completion of treatment, to find out the relapse. After completion of collection of data in a pre-designed & structured questionnaire by interviewing and observing every case, tables were prepared by the observed values, mean and standard deviation were calculated. Levels of significance were tested by independent t-test and chi-square (x2) test. A P value of ≤ 0.05 indicated a significant difference between the two groups.

RESULTS

The majority (48%) of cases were brought to the hospital during the 1st week of illness followed by 29% of patients in the 3rd week or later. Only 23% of patients were brought in the 2nd week of illness. Fever was common to all (100%), followed by headache (63%), anorexia, and nausea (62%), abdominal pain (58%), diarrhea (52%), constipation (29%), and vomiting (8%). Less commonly cough (15%) weakness (8%), jaundice (4%), and bloody diarrhea (2%) were also noted. None of the patients had G.I bleeding or rash. Coated tongue was present in 83% of patients. Hepatomegaly was present in 67% of patients and more common than splenomegaly (42%). Only 42% of patients were visibly toxic looking. Abdominal tenderness was present in 25% of patients, while abdominal distension in 19%. Jaundice was noted in 4% of patients, while caecal gurgling and relative bradycardia in 10% each. Demographic, clinical, and pretreatment laboratory evaluation of the subjects demonstrated that there was no significant difference between the treatment groups. The mean period of defervescence was 5.4±1.09 days for the ceftriaxone group and 4.2+ 0.91 days for the cefixime plus azithromycin group, which is statistically significant. ($p < 0.001$). Duration of therapy was 9.92±4 days in group A and 7±1.12 days in group B, this is statistically significant. ($p < 0.001$). Out of 50 cases in group A, 46 patients become afebrile with ceftriaxone treatment; the success rate is (92%). Out of 50 cases of group B, 2 patients in the cefixime plus azithromycin group failed to respond and the success rate is (96%), which is not statistically significant ($p = 0.399$). The ratio of cost of treatment between ceftriaxone and cefixime plus azithromycin is 9.1: 1, which means that 89% cost reduction is possible in the case of treatment of enteric fever with cefixime plus azithromycin. Gastrointestinal symptoms, notably nausea, vomiting, and abdominal discomfort was the most common adverse effect reported, and more commonly in those treated with cefixime plus azithromycin group than those with ceftriaxone. But this is not statistically significant ($P > 0.05$).

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Table 1: Presenting features of enteric fever (n=100)

Complaints	%
Abdominal pain	58
Headache	63
Diarrhea	52
Constipation	29
Jaundice	4
Vomiting	8
Anorexia & nausea	62
Cough	15
Weakness	8
Bloody Diarrhea	2
Duration:	%
<7 days	48
8-14 days	23
>14 days	29

Table 2: Physical findings of patients. (n=100)

Physical examination	%
Coated tongue	83
Hepatomegaly	67
Splenomegaly	42
Toxic look	42
Dehydration	10
Abdominal tenderness	25
Abdominal distension	19
Jaundice	4
Mouth ulcer	2
Caecal gurgling	10
Relative bradycardia	10

Table 3: Comparisons of demographic, clinical, and pre-treatment laboratory findings (n=100)

Variable	**Group A (Ceftriaxone) n =50**	**Group B (Cefixime plus Azithromycin) n =50**	**p-value**
Age(years) Mean range	 26.2±6.14 (18-53)	 28.5±7.22 (18-60)	0.110
Sex Male Female	 30(60%) 20(40%)	 23(46%) 27(54%)	0.152
Weight (kg) Mean±SD range	 52.2±6.1 (40-74)	 53.1±7.2 (35-75)	0.510
Duration of fever from the dayof enrollment Mean±SD	11.25±2.13	10.52±2.81	0.155
White blood cell/cmm	6200±1236	6600±1125	0.101
S. Creatinine, mg/dl	1.24±.0.31	1.22±0.27	0.737
AST, IU/ml	40.41±7.13	37.89±6.93	0.082
ALT, IU/ml	41.26±3.92	39.82±3.77	0.071
ALP, IU/ml	91.6±10.13	94.6±9.41	0.136

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Table 4: Post treatment clinical parameter (n=50)

Parameter	Group-A	Group-B	P-value
Defervescence from starting treatment, Mean days±SD	5.4±1.09	4.2±0.91	<0.001
Duration of therapy Mean days±SD	9.92±4.0	7.00±1.12	<0.001

Table 5: Treatment outcome (n=100)

Groups	Status of treatment		P-value
	Success	Failure	
Group-A (Ceftriaxone) (n=50)	46 (92%)	4(8%)	0.399
Group-B (Cefixime plus Azithromycin) (n=4508)	48(96%)	2(4%)	

Table-6: Comparison of the treatment cost of an index case of 50 kg body weight (n=100)

	Daily required Dose	Treatment required	Ratio of cost
Group-A (Ceftriaxone)	2 gram 12 hourly (approx. Cost Tk 700/day)	10 days (approx. Cost Tk 7000)	9.1: 1
Group-B (Cefixime plus Azithromycin)	200mg 12 hourly plus 500mg 12 hourly(approx Cost Tk 110)	7 days(approx CostTk 770)	

Table 7: Adverse effects of drugs (n=100)

Parameter	Group-A Ceftriaxone(n=50)No. (%)	Group-B Cefixime plus Azithromycin (n=50)No. (%)	p-value
Nausea	4(8)	5(10)	0.726
Vomiting	4(8)	5(10)	0.726
Abdominal discomfort	0(0.0)	2(4)	0.153

DISCUSSION

In this study, the clinical outcome of a single antibiotic versus a combination of antibiotics in enteric fever was studied. Here single agent was ceftriaxone and the combination of antibiotics was cefixime plus azithromycin. The study was performed to find a less costly, and equally safe and effective oral form of treatment alternative to ceftriaxone. Enteric fever may occur at any age. In this study, the highest prevalence was found between 18-25 years of age (30.20%) followed by 26-33 years of age (23.95%). There is no significant difference in the proportion of sexes in most studies. Our study showed slight male preponderance. The majority (47.92%) of cases were brought to the hospital during the 1st week of illness

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followed by 29.16% of patients in the 3rd week or later. Only 22.92% of patients were brought in the 2nd week of illness. Fever was common in all the cases, followed by headache (63%), anorexia, and nausea (62%), abdominal pain (58%), diarrhea (52%), constipation (29%), and vomiting (8%). Less common symptoms were cough (15%) weakness (8%), jaundice (4%), and bloody diarrhea (2%). G.I bleeding or rash was not present in any of the cases.Coated tongue was present in 83% of patients. Hepatomegaly was present in 67% of patients and it was more common than splenomegaly (42%). 42% of the patients had visible signs of being toxic. Abdominal tenderness was present in 25% of patients, while abdominal distension in 19%. Jaundice was noted in 4% of patients, while caecal gurgling and relative bradycardia in 10% each. In the present study, the patients with enteric fever admitted in the department of medicine fulfilling the inclusion criteria were randomized to receive inj. ceftriaxone 75mg/kg/day for 10 days or until three days from defervescence, whichever one was shorter, as optimal therapy for enteric fever with ceftriaxone is 7-14 days or cefixime plus azithromycin for 7 days.[17,18,25-17]Demographic, clinical, and pre-treatment laboratory evaluation of the subjects demonstrates that both the treatment groups were comparable.The mean period of defervescence was 5.4±1.09 days for the ceftriaxone group and 4.2±0.91 days for the cefixime plus azithromycin group, which is statistically significant. ($p<0.001$). An increase in the duration of the mean defervescence period in our study probably due to indiscriminate use of antibiotics by unregistered practitioners causing reduced susceptibility of the organisms. Another study conducted in our country, with azithromycin, showed a mean defervescence period of 3.82 ±1.49 days.[20] Duration of therapy was 9.92±4 days in group A and 7±1.12 days in group B, this is statistically significant. ($p < 0.001$). Four patients in the ceftriaxone group and two patients in the cefixime plus azithromycin group did not respond, they remained febrile by day 7 and were labeled as a failure. These cases were sensitive to ceftriaxone, cefixime, and azithromycin but failure was probably due to delayed response. After another 5 days of observation in the hospital with the ongoing treatment, they became afebrile. The percentage of success in the ceftriaxone group was 91.67%, while 95.83 % in the cefixime plus azithromycin group but this is not statistically significant. ($p=0.399$) No subject had a serious adverse event. Gastrointestinal symptoms were commonly reported by both groups, which include nausea, vomiting, and abdominal discomfort, which occurred most frequently in subjects treated with cefixime plus azithromycin group may be due to azithromycin. However, the symptoms were mild and transient, resolving in most cases within one day of initiation of treatment. In no case, the symptom was severe enough to require halting the treatment or alteration of antibiotic therapy. The ratio of cost of treatment between ceftriaxone and cefixime plus azithromycin is 9.1:1, which means that

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89% cost reduction is possible in the case of treatment of enteric fever with cefixime plus azithromycin.

Limitations of the study

There were some limitations like unavailability of most of the medical facilities, lack of adequate medical sources and relatively short duration of the study period, and small study sample. Furthermore, this study could have underestimated the nonprescription use of antibiotics in the community, because the study was hospital-based.

CONCLUSION

The irrational use of antibiotics is responsible for the delayed response of enteric fever with common treatment options. So newer treatment options are needed. The treatment of enteric fever with a combination of antibiotics like Cefixime plus Azithromycin is not inferior to a single antibiotic like Ceftriaxone but oral combinations of antibiotics provide a less costly and equally safe and effective oral form of treatment alternative to ceftriaxone. Findings of this were also in accordance with the previous studies with enteric fever. As a small number of patients were studied so findings of this study should be cautiously extrapolated into the broader context.

Recommendations

Further research work could be recommended to evaluate the impact of a combination of antibiotics in the treatment of enteric fever. Seminars and workshops could be arranged in the cities, Upazilla, and unions to stop indiscriminate use of antibiotics. Mass media can help to build public awareness to decrease the indiscriminate use of antibiotics.

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