RESEARCH

A Comparative Study Between Cefixime and Ofloxacin in The Treatment of Uncomplicated Typhoid Fever Attending A Tertiary Care Teaching Hospital

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ABSTRACT

Background: Typhoid fever is a gastrointestinal infection caused by Gram-negative bacterium *Salmonella enterica serovar typhi (S.typhi)*. Typhoid fever continues to be one of the major public health problems in developing countries. Antimicrobial therapy is critical for the clinical management of enteric fever. Incidences of multi-drug resistance to S. typhi (MDRST) and nalidixic acid resistant (NAR) strain have limited treatment options. Resistance pattern and time to fever clearance vary in different geographical areas and overtimes. Hence, this study was conducted to compare efficacy and safety profile of Cefixime and Ofloxacin in uncomplicated typhoid fever in this region.

Method: 50 adults proven cases of typhoid fever of the age group of 18-57 years of either sex were included in the study. Group I was treated with Cefixime 200 mg twice a day for 7 days and CG I was treated with Ofloxacin 200 mg twice a day for 7 days. Patients were clinically and bacteriologically evaluated during the study period and follow-up.

Result: So both study groups were found comparable in terms of mean fever clearance time. 96% cure rates were observed in both groups. No relapse was recorded.

Conclusion: Both Cefixime and Ofloxacin are equally efficacious and safe in the treatment of uncomplicated typhoid fever.

Keywords: Cefixime, Ofloxacin, Typhoid fever

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INTRODUCTION

Typhoid fever referred to as infectious disease, commonly known as enteric fever, caused by the gram-negative bacteria, Salmonella enterica serover typhi that occurred through consumption of food or water contaminated with feces of an infected person. The mode of transmission of disease is mainly the feco-oral route and thus high incidence has been found in this part of the world because majority of persons are still consuming unsafe water due to lack of facility of water supply and weak sanitation substandard.[1,2]

Typhoid fever is estimated to cause over twenty-six million infections and over 0.2 million deaths annually worldwide. However, South-central Asia and south-east Asia have been identified as regions with high incidence of typhoid fever (>100/100,000 cases/year), whereas the rest of Asia,

Africa, Latin America and Oceania excluding Australia and New Zealand have reported a medium incidence (10-100 / 100.000 cases/year).[3] Moreover, typhoid fever was infrequently reported in the developed countries; mainly occurred to travelers getting back from endemic areas while it was not domestically acquired disease.[4]

Salmonella enterica serotype typhi is the aetiological agent of typhoid fever, a multisystemic disease with protean manifestations and initial lesions in the bowel. Salmonella typhi is a gram-negative non-spore bearing organism that is motile by means of flagellae. They can survive long periods in hot, humid environment and withstand freezing. Infective dose is about 105- 109 organism, with an incubation period ranging from 4-14 days.[5]

Typhoid fever is characterised by malaise, fever, abdominal discomfort and tenderness, transient rose colour eruptions, splenomegaly, sometimes hepatomegaly, pea - soup diarrhoea or sometimes constipation, toxaemias and leucopenia. The confirmatory diagnosis could be made by blood culture, antityphoid IgM test, widal test, stool culture, depending upon course of systemic manifestation. However, with the development of newer antimicrobial agents and improvement in sanitation have shown shortens the clinical course of typhoid fever and reduces the risk of death. (Please give the reverence). But shortly multi-drug resistance to *S typhi* (MDRST) was developed to all three first line antibiotics (Chloramphenicol, Ampicillin and Co- trimoxazole). Recently, the newer drugs have been recommended in the treatment includes Cefixime, Ofloxacin, Azithromycin and injectable third generation Cephalosporins.[6, 7, 8]

Cefixime, third generation Cephalosporin, exert bactericidal activity by interfering with bacterial peptidoglycan synthesis after binding to the β-lactam-binding proteins. The Cephalosporins are also thought to play a role in the activation of bacterial cell autolysins which may contribute to bacterial cell lysis.[9] Ofloxacin, first generation Fluoroquinolones, act by inhibiting DNA gyrase, an enzyme necessary to separate replicated DNA, thereby inhibiting bacterial cell division. In vivo, ofloxacin has excellent intracellular penetration.[10] The quick development of resistance stains bacteria is the real problem in Indian subcontinent; ample of studies isolated fully resistant to Fluoroquinolones due to mutations in the gyrA gene and occasionally the parC gene[11] and the extended spectrum Cephalosporins[7]. Comparative efficacy of these options in the adult is few and a single study reported a shorter defervescence time with the use of Ofloxacin when compared to Cefixime.[12] Variation in nalidixic acid resistant (NAR) pattern and fever clearance time varies between drugs in different geographical areas and over time.[12-13] The purpose of this study was to compare the efficacy and safety of Cefixime and Ofloxacin in uncomplicated typhoid fever in this region.

METHOD

The present prospective study was carried out in National Medical College & Teaching Hospital, Birgunj, Nepal, during the period from June 2016 to January 2017 after obtaining approval from intuitional ethical committee.

Fifty patients diagnosed with Typhoid fever were selected in this study; the diagnosis was based on clinical and at least one lab criteria. The inclusion and exclusion criteria were made, listed below:

Inclusion Criteria

- Adults of either gender, above 18 years of age and able to take oral medication.
- Fever ≥3 days.
- Lab criteria included positive blood culture positive for S.typhi, tube widal (O>1:80 & H>1:160) & positive anti-typhoid IgM test.
- Willing to give written informed consent to take part in the study.
- Patient able to take oral medication.

Exclusion Criteria

- Pregnant or lactating women.
- Unable to swallow oral medication
- Allergy to cephalosporins or fluoroquinolones
- Typhoid fever associated with complication e.g. presence of jaundice, gastrointestinal bleeding, shock, encephalopathy, arrhythmia
- Treatment within the past with an antibiotic that may be effective against typhoid fever

The study subjects (patients) were randomly assigned into two groups: Cefixime Group (CG) and Ofloxacin Group (OG). Each group was contained 25 patients and all the subjects were prescribed either Cefixime 200mg or Ofloxacin 200mg, per oral twice in a day for 7 days.

The patients were examined twice daily (morning & evening) to perform a simple clinical assessment measure the oral temperature until day 7. The progress of the cases was recorded with special reference to a period of defervescence of fever and general condition. Discharge criteria were the clinical improvement & an afebrile period of at least 24 hrs. All cases were followed up once weekly up to 4 weeks. Fever clearance time, cure rate, and recurrence of the symptom of relapse were evaluated. Patients were monitored continuously throughout the study for any adverse drug reaction (ADR). Safety monitoring was done continuously throughout the study. All ADR spontaneously reported by the subjected or elicited by the investigators were recorded.

Following parameters were included:

A) Fever Clearance Time (FCT), defined as time to first drop in oral temperature ≤ 37.5°C, remaining ≤ 37.5°C for 48 hours.
B) Cure rate, the patient were considered clinically cured when fever subsided within 7 days of antibiotics therapy and without any clinical relapse during four weeks follow-up period.
C) Adverse drug reaction.
D) Relapse, defined as fever with a positive blood culture within a month of completing treatment.
E) Therapeutic failure, defined as persistence of fever after 7 days of treatment or development of complication under the treatment.

STATISTICAL ANALYSIS

Data were presented as mean and standard deviation using an SPSS software version 15.0. Student paired T-test were applied for the comparison of different variables between both groups with p-value <0.05 was considered significant.

RESULT

Out of 50 patients, 34 were male and 16 were females in the range of 18-57 years. Both groups were comparable in terms of age (mean age 26.44 ± 8.7 years for the CG v/s 27.16 ± 8.4 years in OG) [Table1] and duration of fever before starting treatment (mean duration of fever 8.76±3.6 days for CG v/s 8.68±3.8 for OG). There was not much difference between 2 groups in terms of clinical symptoms and signs as well as the severity of illness and laboratory findings.

Table 1 : Showing Age and Sex incidence in the two groups

Age group (in Year)	Cefixime (CG)						Ofloxacin (OG)					
	Male		Female		Total		Male		Female		Total (%)	
	n	%	n	%	n	%	n	%	n	%	n	%
18-25	12	48	2	8	14	56	9	36	4	16	13	52
26-33	2	8	2	8	4	16	4	16	3	12	7	28
34-41	4	16	2	8	6	24	1	4	0	0	1	4
42-49	0	0	0	0	0	0	2	8	2	8	4	16
50-57	0	-0	1	4	1	4	0	0	0	0	0	0
Total	18	72	7	28	25	100	16	64	9	36	25	100

Mean age for CG: 26.44±8.7 yrs
Mean age for OG: 27.16±8.4 yrs

Mean fever clearance time for CG was 4.75±0.6 days were as in OG was 4.50±0.8 days [Table 2]. There were no statistically significant differences in the fever clearance time between the two groups. So the two groups were found to be comparable in term of mean fever clearance time at the end of the study.

Table 2 : Showing mean clearance time in two groups (p>0.05)

Groups	Mean fever clearance time ±SD (in days)
CG	4.75±0.6
OG	4.50±0.8

SD: Standard derivation

The patient was considered clinically cured when fever settles within seven days of antibiotic therapy and without any clinical relapse during four weeks follow-up period. In both group cure was found to be 96% [Table3].

Table 3 : Showing response to therapy in two groups

	Total cases	Good*	Moderate**	Poor***	No response	Relapse
CG	25	1(4%)	21(84%)	2(8%)	1(4%)	-
OG	25	2(8%)	21(84%)	1(4%)	1(4%)	-

*Temperature settling in 3 days,**Temperature settling in 3-5 days,***Temperature settling in >5 days

One (4%) from each group did not responded even after 7 days treatment and was considered treatment failure. No relapse was recorded in the present study in a follow-up period of 4 weeks in both study groups. Three patients (16%) from both groups experienced minor adverse effect like nausea, pain abdomen and were managed easily.

DISCUSSION

Typhoid fever is a communicable disease and occurs due to systemic infection mainly by Salmonella typhi organism. For the management of typhoid fever, rapid cure is desirable to prevent the acute and chronic complications of Salmonella infection. Drug resistance among *S. Typhi* and *Salmonella Paratyphi* poses a major challenge in the management of typhoid fever. Emergencies of MDRST has restricted to all three first line drug (Chloramphenicol, Ampicillin and Cotrimoxazole). Second-line antibiotics like third generation Cephalosporins, Fluoroquinolones and Azithromycin are used for treating MDR typhoid fever. Cephalosporin class of drugs suffers from poor cellular penetration leading to poor overall clinical outcome indicators seen as long fever clearance time. Alternate drug regime such as monotherapy ofloxacin is also suggested. Several studies using Ofloxacin, show shorter defervescence time, reduced clinical failure and relapse when compared to cefixime.[12] Safety about joint damage has been laid to rest. However, other studies have suggested cefixime can be successful in the treatment of typhoid fever.

DCGI (Drug controller General of India) approved (26/04/2010) combination of Cefixime with Ofloxacin in the management of typhoid fever. Cephalosporins and Fluoroquinolones act through a different mechanism, they provide rapid bacteriological eradication.

Resistant to Fluoroquinolones due to mutations in the gyrA gene and occasionally the parC gene has been reported in some studies[11] and the extended spectrum Cephalosporins[7].

Variation in nalidixic acid resistant (NAR) pattern and fever clearance time varies between drugs in different geographical areas.

Our study show equal efficacy with both Ofloxacin and Cefixime in typhoid fever. Cefixime is an effective alternative in condition were ofloxacin is contraindicated i.e. children. Larger studies are required to assess the comparative efficacy of various drugs in Typhoid fever and changing pattern of MDRST and NAR strains.

CONCLUSION

Both Cefixime and Ofloxacin are equally efficacious and safe in the treatment of uncomplicated typhoid fever.

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Conflict of Interest: None

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