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Research Article

ORAL CEFIXIME VERSUS ORAL CO-TRIMOXAZOLE IN THE TREATMENT OF UNCOMPLICATED TYPHOID FEVER IN CHILDREN (1-14 YEARS): A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: The typhoid fever caused by salmonella typhi remains a serious problem in developing countries like India. It is estimated that more than 26.9 million typhoid fever cases occur annually out of which 1% result in death.

Objectives: To compare efficacy of oral Cefixime with oral Co-trimoxazole to treat uncomplicated typhoid fever in children.

Materials and Methods: This prospective double blinded randomized control trial was conducted in Paediatric ward at belagavi institute of medical sciences, Belagavi from January 2019 to December 2019. Children aged 1-14 years with uncomplicated typhoid fever after positive Widal test, were randomly allotted into one of the two groups of intervention as per computer generated random number table. One group received oral Cefixime 20 mg/kg/day in two divided doses and another group received oral Co-trimoxazole 10mg/kg/day of Trimethoprim in two divided doses. Patients monitored every 6th hourly for defervescence of fever and other symptoms. “Clinical cure” was considered as resolution of symptoms by the

end of 5 days of treatment. "Clinical failure" was defined as persistence of 1 or more typhoid related symptoms.

RESULTS: Eighty patients with positive WIDAL tests enrolled in the study. Mean duration for defervescence of fever was 75.94(±12.12) hours in Cefixime group compared to 79.24(±10.92) hours in Co-trimoxazole group but difference was statistically not significant (p-0.693). 33 out of 40 (82.50%) patients responded in Cefixime group as compared to 27 out of 40 (72.50%) in Co-trimoxazole group. Clinical cure was comparable and difference was statistically not significant (p-0.284).

CONCLUSION: Oral Co-trimoxazole can be considered as an effective alternative to oral Cefixime in treatment of uncomplicated typhoid fever in children between 1 to 14 years.

KEYWORDS: Typhoid Fever; Cefixime; Co-trimoxazole; Defervescence; Clinical Cure; clinical failure.

INTRODUCTION

The typhoid fever caused by salmonella typhi remains a serious problem in developing countries like India. It is estimated that more than 26.9 million typhoid fever cases occur annually out of which 1% result in death. These figures are representing the clinical syndrome rather than the culture proven typhoid fever cases. The typhoid infection is predominantly seen in school age. However, this infection is reported to be milder in infants and very young children. There is a wide range of presentation with involvement of various organs.[1]

Since 1990's, S. Typhi has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin).[2] 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. The beta

lactams such as cefixime and ceftriaxone are now being increasingly used, but these are expensive drugs and are associated with a long time to defervescence. Recently, azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever (World Health Organization, 2003; Parry et al., 2002).[3] The fluoroquinolones, other second-line antibiotics, such as third-generation cephalosporins (eg, ceftriaxone and cefixime), and azithromycin are currently regarded as the antibiotics of choice for treating MDR strains. However, an issue of great concern is the emergence of strains of S. Typhi and S. Para typhi with reduced susceptibility to fluoroquinolones.[2] Since 1990's, S. Typhi has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin).[2] 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. The beta lactams such as cefixime and ceftriaxone are now being increasingly used, but these are expensive drugs and are associated with a long time to defervescence. Recently, azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever (World Health Organization, 2003; Parry et al., 2002).[3] The fluoroquinolones, other second-line antibiotics, such as third-generation cephalosporins (e.g., ceftriaxone and cefixime), and azithromycin are currently regarded as the antibiotics of choice for treating MDR strains. However, an issue of great concern is the emergence of strains of S. Typhi and S. Para typhi with reduced susceptibility to fluoroquinolones.[2]

In recent years, the epidemiology and drug resistance profile of salmonella strains causing enteric fever has changed. The shift towards reemergence of susceptibility patterns towards former first-line antibiotics

(e.g.: ampicillin, co-trimoxazole, and chloramphenicol) seen in many studies could be explored as an option for drug treatment. Investigators of a north Indian study reported a statistically significant decrease in antimicrobial resistance to former first-line antibiotics among the 852 *Salmonella enterica* serotype Typhi isolates over a 12-year period. They further reported that, in 2012, more than 95% *Salmonella* Typhi clinical isolates were susceptible towards each of these former first-line antibiotics.[4] Findings from a study from Nepal during 2011–12 of 86 salmonella isolates showed a high degree of susceptibility to former first-line antibiotics (100% susceptibility to chloramphenicol and co-trimoxazole, and 98.2% susceptibility to ampicillin).[5]

The re-emergence of drug-susceptible strains might result from lack of antibiotic pressure since these drugs are not being used routinely. This possibility has also been suggested by Dutta and colleagues, who proposed that the re-emergence of susceptibility to these drugs might result from the emergence of de-novo susceptible strains or the loss of high-molecular weight self-transmissible plasmids. [6,7]

Recent studies on antibiotic sensitivity pattern have shown promising results towards earlier first line antibiotics like Chloramphenicol, Co-trimoxazole and Ampicillin. [2] Only limited studies available. So, the study was designed to compare the efficacy of oral cefixime with oral co-trimoxazole in the treatment of uncomplicated typhoid fever in children (1-14 years).

MATERIALS AND METHODS

The study was a Prospective double blinded randomized controlled trial included patients of age group 1-14 years admitted to Paediatric ward at BIMS, Belagavi over a period of one year from January 2019 to December 2019 with proven Typhoid fever cases.

INCLUSION CRITERIA:

1] The Children aged 1 to 14 years who are suspected of having typhoid fever admitted in the pediatric ward with documented fever (axillary temperature > 37^0C) for ≥ 5 days [4] with

2] A Positive Widal test or Raising titres of O or H antigens. (O agglutinins ≥ 1**:**160 or H agglutinins ≥ 1 **:**160 by tube agglutination type of widal test or 4-fold raise at 1wk apart) [5] or

3] Blood culture positive for Salmonella typhi.[1]

EXCLUSION CRITERIA:

1] Complication of Typhoid Fever; Encephalopathy, cerebral edema, endocarditis, myocarditis, pneumonia, osteomyelitis, septic arthritis, cholecystitis, hepatic abscess, intestinal obstruction or perforation and internal hemorrhage.[1]

2] Significant illness with inability to swallow oral medication.

3] Known allergy to cefixime, co-trimoxazole

4] Hemodynamically unstable patients.

5] Typhoid vaccinated patients.

6] Lack of parent Consent.

7] Those who received antibiotics prior to hospital visit.

Total 80 eligible patients were enrolled after obtaining clearance from Institutional ethical committee and informed written consent from either of parents. The study group was divided into two groups randomly by computer generated random number table. One group received oral Cefixime (20

mg/kg/day) in two divided doses up to maximum 400 mg/day. Another group received oral Co-trimoxazole (10 mg/kg/day of Trimethoprim in two divided doses) up to maximum 320 mg /day of Trimethoprim (Co-trimoxazole is a fixed dose combination of trimethoprim and sulfamethoxazole at 1:5) [6,7]

Blinding was done by giving the drug after masking the label and thus both groups appeared similar. Children under 5 years of age were given Syrup form, between 5 to 14 years were given tablet form.

Both the groups received symptomatic treatment (antipyretic, antiemetic, IV fluid) [1] till either of blood culture or widal test became positive, after which antibiotics also started. If symptoms including fever and signs were not controlled with either of drugs in 5 days then it was considered as treatment failure.[7] Then next line of drug given was IV ceftriaxone (75 mg/kg/day) in two divided doses was given for total duration of 7 days.[1]

During hospitalization, clinical examination of all patients was performed daily with a pre structured proforma. The vital parameters (heart rate, blood pressure, respiratory rate and body temperature) measured sixth hourly. Response to treatment was defined as subsidence of symptoms (including fever) and signs within 5 days of administering either of the drugs. All responders, corresponding drug was given for total duration of 10 days. All non-responders were given IV ceftriaxone (75 mg/kg/day) for total duration of 7 days.

“Clinical cure” was considered as the resolution of symptoms and signs by the end of 5 days of treatment. “Clinical failure” was defined as persistence of 1 or more of typhoid related symptoms (Symptoms like fever, anorexia, vomiting, diarrhea, headache, jaundice, abdominal pain, constipation) which were present at the beginning of study in the subject, even after 5 days.

Just before commencement of drug therapy, specimen of blood was obtained from children for the following investigations. Complete blood count, platelet count, blood culture and sensitivity, dengue serology (NS1 antigen, IgM antibodies) Peripheral smear for malarial parasite. 5 ml of venous blood withdrawn under asceptic precautions and collected in culture bottle (Brain Heart Infusion broth) and cultured by Conventional method (Mac Conkey agar).

Anemia was defined as per age based cut off values (if value is < 105 g/L in 1 to 23 months, 115 g/L in 2 to 9 years, 125 g/L in 10 to 17 years of males and 120 g/L in females of 10 to 17 years). leucocytosis was defined as per age based cut off values (if value is > 14 $\times 10^9$ cells/L in 1 to 23 months, 12 $\times 10^9$ cells/L in 2 to 9 years and 10.5 $\times 10^9$ cells/L in 10 to 17 years), lymphocytosis is defined if value is >40% and thrombocytopenia as value of < 150×10^9 cells/L.[1] Widal Test (Tube Agglutination Test) after duration of fever more than or equal to 7 days. Urine routine and microscopy, 5 ml of midstream urine sample is collected under aseptic precautions in container for urine analysis.

STATISTICAL ANALYSIS:

In the present study, statistical methods were applied for quantitative data and qualitative data. Quantitative data was presented by n, Mean, Standard Deviation and Range. For qualitative data, frequency count n and percentage were tabulated in tables. To analyze the data, appropriate statistical tests were applied. To compare the difference between two means, nonparametric Mann Whitney U test and independent t test was used. Statistical significance is considered if p value is < 0.05.

All the statistical analysis has been done by using statistical software SPSS (version 26.0). Other data was displayed by various tables and charts by using Microsoft excel (windows 10).

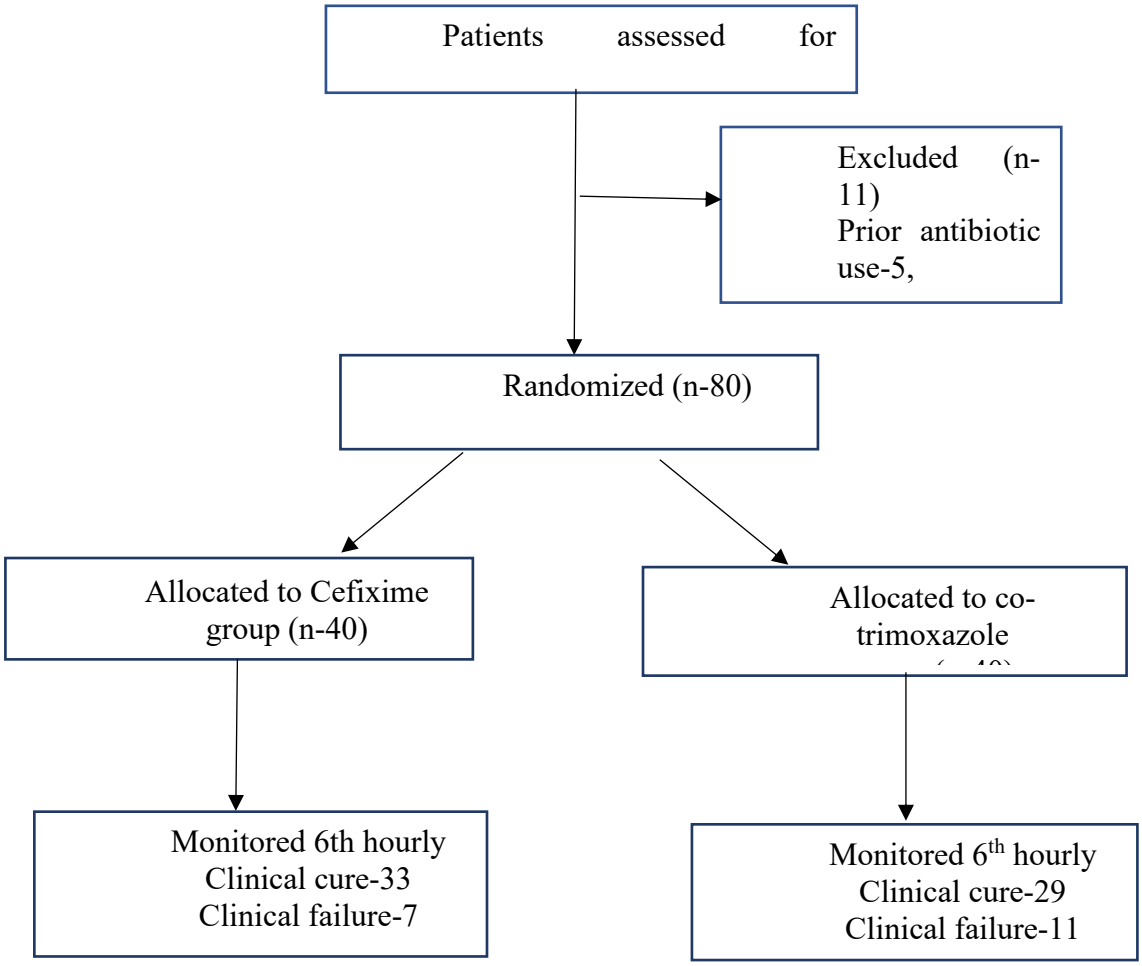

FIGURE-1 Flow chart of participants in the study

RESULTS

On analysis of 80 cases of clinical typhoid fever with positive widal test after excluding 11 cases (5 cases are excluded as they received antibiotics before widal report, 3 cases denied consent and 3 cases whose age more than 14 years are excluded) at the time of admission in pediatric ward, BIMS, the following observations were drawn.

Majority of patients were of age group >5 - 10 and >10 - 14 years 38.50% and 41.25% respectively. Mean age of cases in Cefixime group was 9.47(±3.56) years and Co-trimoxazole trial group was 9.13(±3.66) years. Overall gender wise distribution, Male: Female ratio was 1.28:1 with ratio of 1.22:1 in Cefixime trial group and 1.35:1 for Co-trimoxazole trial group.

Analysis of demographic characteristics revealed statistically not significant differences (p value for age comparison - 0.969 and for gender comparison - 0.822) between patients treated with cefixime trial group and co-trimoxazole trial group.

Cases were compared as per socioeconomic strata between two groups and found majority of cases in class IV and V as per modified BG Prasad classification of socioeconomic status, 25(62.5%) and 13(32.5%) cases in cefixime group as compared 15(37.5%) and 18(45%) in co-trimoxazole group in respectively. Statistically not significant difference found, p value - 0.177.

Anthropometric measurements was done in our study where we assessed head circumference, chest circumference in less than 5 years and weight for age, height for age and weight for height in all other cases and found majority of cases within median and between median and -1SD, 15(37.5%) and 24(60%) in cefixime group as compared to 12(30%) and 23(57.5%) in co-trimoxazole group respectively. Statistically not significant difference found, p value - 0.368.

Cases in both groups presented with fever as their main complaint, present in all cases. Pain abdomen (37.50%) was the second most common symptom noted in study subjects followed by vomiting (30%), loose stools (20%), cough (18.75%), headache (8.75%) and anorexia (8.75%). Analysis of pattern of symptoms revealed statistically not significant difference between two groups (table I).

TABLE I: ANALYSIS OF SYMPTOMS AMONG STUDY SUBJECTS

SYMPTOMS	CEFIXIME GROUP n (%)	COTRIMOXAZOLE GROUP n (%)	TOTAL n (%)	P VALUE
FEVER	40(100)	40(100)	80(100)	1.0
VOMITING	11(27.50)	13(32.50)	24(30)	0.626
PAIN ABDOMEN	15(37.50)	15(37.50)	30(37.50)	1.0
LOOSE STOOLS	8(20)	8(20)	16(20)	1.0
COUGH	10(25)	5(12.50)	15(18.75)	0.152
HEADACHE	3(7.5)	4(10)	7(8.75)	0.692
ANOREXIA	2(5)	5(12.50)	7(8.75)	0.235

*Statistically not significant difference between two groups, p value > 0.05.

Most common sign noted among study subject was hepatomegaly (52.50%) followed by abdominal tenderness (37.50%), coated tongue (32.50%) and splenomegaly (23.75%). Statistically not significant difference found between two groups, p value > 0.05.

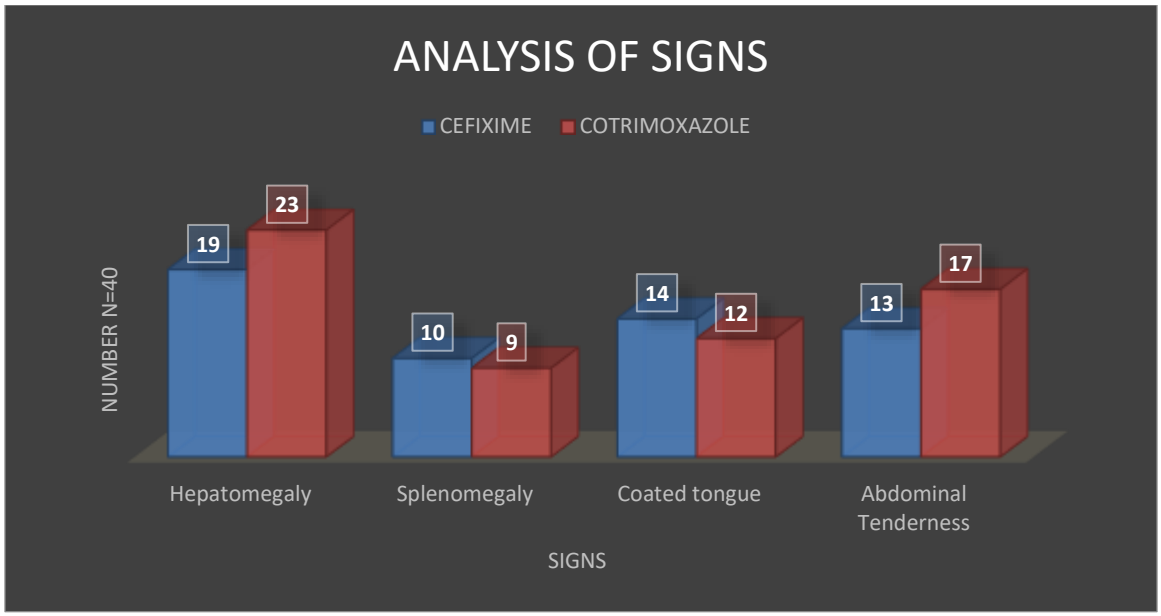

FIGURE I: ANALYSIS OF SIGNS AMONG STUDY SUBJECTS

Analysis of pretreatment laboratory results revealed no statistical significance between two groups. Mean (SD) of hemoglobin (g/L), TLC ($\times 10^9$/L) and platelet counts ($\times 10^9$/L) were 104.9(±16.92), 7.31(±2.44) and 250(±89.10) in Cefixime trial group; 102.9(±19.95), 6.68(±2.08) and 236(±94.3) respectively in Co-trimoxazole trial group. Mean neutrophil, lymphocyte and eosinophil counts were 55.67 %, 39.52% and 2.75% respectively in Cefixime trial group; 54.52%, 40.62% and 2.90% respectively in Co-trimoxazole trial group. None of the cases shown blood culture positivity. Most common lab abnormality seen was anemia and seen in 60% of cases followed by relative lymphocytosis in 37.50%, leukocytosis in 6.25%, and thrombocytopenia in 11.25%. dengue co infection was seen in 18.75% cases.

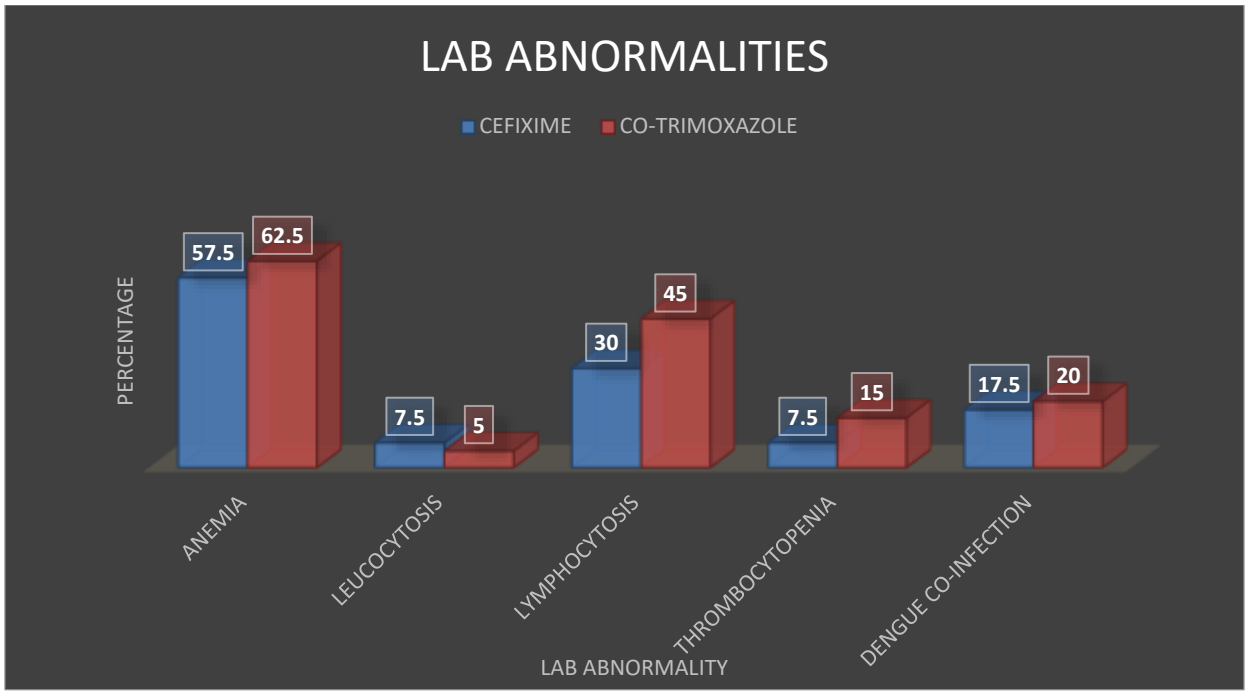

FIGURE II: ANALYSIS OF LAB ABNORMALITIES

Clinical cure was occured early with cefixime treatment as compared to co-trimoxazole. Defervesence of fever started as early as 48 hours in patients treated with cefixime as compared to 60 hours in cotrimoxazole group. Among responders, defervescence of fever occurred maximum within 96 hours in both the groups. Mean duration of response in cefixime group was 75.93±12.12 hours and 79.24±10.92 hours in co-trimoxazole group respectively, which was statistically not significant (p-0.693).

Among patients who received cefixime 33 out of 40 (82.50%) responded for the treatment as compared to 29 out of 40 (72.50%) in co-trimoxazole group. 9 (17.50%) cases in cefixime group were non responders as compared to 11 (27.50%) in co-trimoxazole group. Clinical cure was similar in both the groups and difference was statistically not significant, p value is 0.284 (Table III).

TABLE II: DESCRIPTIVE STATISTICS FOR CLINICAL RESPOSE

DURATION OF RESPONSE (Hours)	CEFIXIME GROUP	COTRIMOXAZOLE GROUP
MEAN	75.94	79.24
MEDIAN	78.00	84.00
STANDARD DEVIATION	12.12	10.92
RANGE	48	36
INTERQUARANTILE RANGE	12	18
MINIMUM	48.00	60.00
MAXIMUM	96.00	96.00
95% CONFIDENCE INTERVAL FROM MEAN	71.64 80.24	75.09 83.40
STANDARD ERROR MEAN	2.110	2.028

DISCUSSION

Typhoid fever is a common illness of children and young adults thus having significant socioeconomic impact on the community. The developed countries have controlled this illness by improving standards of public health; but the disease continues to be a major public health problem in developing countries like India.

In recent years, the epidemiology and drug resistance profile of salmonella strains causing enteric fever has changed. The shift

towards reemergence of susceptibility patterns towards former first-line antibiotics (eg: ampicillin, co-trimoxazole, and chloramphenicol) seen in many studies could be explored as an option for drug treatment. Investigators of a north Indian study reported a statistically significant decrease in antimicrobial resistance to former first-line antibiotics among the 852 *Salmonella enterica* serotype Typhi isolates over 12 years period. They further reported that, in 2012, more than 95% *Salmonella* Typhi clinical isolates were susceptible towards each of these former first-line antibiotics. Findings from a study from Nepal during 2011–12 of 86 salmonella isolates showed a high degree of susceptibility to former first-line antibiotics (100% susceptibility to chloramphenicol and co-trimoxazole, and 98.2% susceptibility to ampicillin).[9]

The re-emergence of drug-susceptible strains might result from lack of antibiotic pressure since these drugs are not being used routinely. This possibility has also been suggested by Dutta and colleagues, who proposed that the re-emergence of susceptibility to these drugs might result from the emergence of de novo susceptible strains or the loss of high-molecular weight self-transmissible plasmids. [8]

There is need to reconsider the use of former first line antibiotics for treatment of uncomplicated enteric fever. So, the study was designed to compare the efficacy of oral cefixime with oral co-trimoxazole in the treatment of uncomplicated typhoid fever in children admitted to pediatric ward, Belagavi Institute of Medical Sciences, Belagavi.

ANALYSIS OF DEMOGRAPHIC CHARACTERS

a] Age and sex

In our study, cases were predominantly seen in the age group of >5 to 10 and >10 to 14 years of about 38.50%

and 41.25% respectively. Gender wise distribution male: female ratio was 1.28:1. In a study conducted by Ramasamy et al, male: female ratio was 1.29:1. Most common age group affected was 5-10 yrs (33.5%) with 1.8 % cases in less than 1 year of age, 16 % cases between 1-2 years, 32 % cases between 2-5 years and 15.8 % cases more than 10 years of age. In a study conducted by Ranganatha et al cases were predominantly in age group of 5-14 years with male: female ratio of 1.75 :1. Adithya et al found 53(58.24%) of the 91 study patients were males and 38(41.75%) were females. Mean age of the study group was 7.74 years.

ANALYSIS OF CLINICAL PROFILE:

a] Symptoms

Most common symptom in our study was fever, found in all cases followed by Pain abdomen (37.50%) was the second most common symptom noted in study subjects followed by vomiting (30%), loose stools (20%), cough (18.75%), headache (8.75%) and anorexia (8.75%). while Ranganatha A et al found fever as the main symptom of presentation (100%) followed by anorexia (61%), vomiting (44%) and pain abdomen (18%). Adithya et al found fever as main symptom followed by abdominal pain (53.85%), vomiting (41.76%) and diarrhoea (19.78%).

None of the cases in our study had history of documented typhoid fever in the past, No cases had previous history of congenital heart diseases, epilepsy, tuberculosis and asthma.

b] Socioeconomic class

We classified cases into various socioeconomic class as per modified BG prasad classification which again based on the Per capita income of the family. About 50% cases were in class IV and 38.75% in class V category.

c] Nutritional assessment and clinical signs

Head to toe examination of all the cases revealed no abnormal findings except pallor was noticed in 60% cases. Anthropometric evaluation of all subjects was done in our study where we assessed weight for age, height for age and weight for height in all cases and found 33.75% in median and 58.75% in between median and -1SD.

Most common sign noted among study subjects was hepatomegaly (52.50%) followed by abdominal tenderness (37.50%), coated tongue (32.50%) and splenomegaly (23.75%). While Ranganatha et al found toxic look in 68% cases, 49% cases coated tongue and hepatomegaly in the 44% cases.

In our study examination of other systems including cardiovascular system, respiratory system and Central Nervous system revealed no abnormality. No side effects or adverse complications encountered during or after the treatment among both the groups.

Analysis of laboratory parameters

Widal test by tube agglutination type used as main diagnostic test in this study, whereas blood culture and Widal test together used as diagnostic test in studies conducted by Ranganatha A et al, Ramaswamy et al and Adithya et al. No statistical significant differences was found in the mean values of laboratory parametres between Cefixime and Co-trimoxazole group.

Most common laboratory abnormality noticed was Anemia in 60% of cases followed by relative lymphocytosis in 37.50%, leukocytosis in 6.25% and thrombocytopenia in 11.25%. Dengue co infection was seen in 18.75% cases. While Ranganatha et al found anemia in 16% cases and thrombocytopenia in 15 % cases. Adithya et al found mean WBC count of 8395 cells/cumm. Out of 91 patients, 72(79.12%) had WBC count within the normal range. 3(3.29%) had leucopenia, while 16(17.58%) had leucocytosis. 4(4.39%) had

thrombocytopenia. Absolute eosinopenia was found in 11(12.08%).

Blood cultures are sterile in all cases, which may be due to usage of conventional methods for culture. Ranganatha et al found 20% blood culture positivity for the salmonella. None of the cases had malarial parasite on peripheral smear examination.

We monitored all the cases every 6th hourly for heart rate, respiratory rate, blood pressure and temperature for fever defervescence. We checked for persistence of any of the symptoms which present at the time of enrollment during hospital stay for 5 days. Continued the drug in responsive cases for 10 days.

Our study included 80 patients of febrile illness with WIDAL positive typhoid fever, 62 (77.50%) children attained clinical cure within 5 days, while 18(22.50%) failed. In the Cefixime group, 33(82.50%) children attained clinical cure in 5 days and 7(17.50%) failed. In the Co-trimoxazole group, 29(72.50%) children achieved clinical cure in 5 days and 11(27.50%) failed. Difference in proportion of patients achieving clinical cure was statistically not significant (p value was 0.284).

In a study Nawaz et al found, 28 cured out of 30 patients successfully, with an efficacy of 93.3% with oral cefixime. In a study by Pandurang et al, 100 percent cases showed bacteriological cure with Cefixime. Chaudhary et al found clinical cure in 98/112 (92.5%) subjects. The efficacy was measured as absence of symptoms on 10th day of treatment. No serious adverse events observed.

Our study has shown that 10 days course of oral Co-trimoxazole is an effective alternative treatment to oral Cefixime for uncomplicated typhoid fever in children between 1-14 years. The average defervescence time was 75.94±12.119 hours with Cefixime as compared to Co-trimoxazole was 79.24±10.921 hours.

However, this was statistically not significant (p-0.284). In Marwa et al study temperature defervescence achieved within 3.9 ± 1.4 days with oral Cefixime. Fever cleared in 10% of cases on the second day. 40% of patients had no fever after 3 days of treatment, 76.7% of cases cured after four days. Fever cleared collectively in 90% of the patient by 5 days.

The limitation of our study was the small size of sample. Further studies are required to know the sensitivity pattern, cure rates and relapse rates associated with co-trimoxazole. Some patients with typhoid fever are unable to swallow oral preparations or have vomiting either due to the medication or illness, this may also limit its use as an OPD treatment.

CONCLUSION: Our study has shown clinical cure was similar in both the groups and difference was statistically not significant (p value is 0.284). So, Co-trimoxazole can be used as an effective alternative to Cefixime in the treatment of uncomplicated Typhoid fever, which is cost effective. This would remain an advantage in treatment of uncomplicated typhoid fever in children in the era of antibiotic stewardship

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WHAT IS ALREADY KNOWN?

Ceftriaxone and Cefixime are the standard of care in the treatment of typhoid fever.

WHAT THIS STUDY ADDS?

Co-trimoxazole can be used as an effective alternative to Cefixime in the treatment of uncomplicated Typhoid fever in children.

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