www.jmscr.igmpublication.org Impact Factor 3.79
ISSN (e)-2347-176x

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Comparative Study of Efficacy of Ciprofloxacin and Ceftriaxone in Typhoid Fever

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ABSTRACT

Typhoid fever is an acute systemic disease. It is caused by Salmonella typhi. The disease is unique to humans. In 1880, Ebreth first isolated the causative organism. The disease has worldwide in distribution and endemic in Tropical Countries. Between 15 and 35 years of age incidence of disease is more. Typhoid had been prevalent in many parts of India and is resistant to chloramphenical, ampicillin, co-trimaxazole. The use of quinolones in children has been prevalent. The Ciprofloxacin used in children are not free from adverse effects.

The resistant cases requires Cephalosporins. Currently the III generation cephalosporins like ceftriaxone and cefotaxime are used in multi drug resistant typhoid fever. These drugs are bactericidal and are very effective.

The aim of the present study is to compare the efficacy Ciprofloxacin and Ceftriaxone in treatment of Typhoid fever. Patients who attended the department of Medicine with fever were selected. They were divided into two groups.

25 patients were treated with ceftriaxone under Group – I and another 25 patients were treated with Ciprofloxacin under Group – II. The results of both groups were recorded. There were significant differences observed among patients in the two groups with regard to age, sex, duration of fever before admission and clinical findings. The mean number of days for patients to become afebrile was significantly lowered in those receiving ceftriaxone ($P < 0.001$) than in those receiving Ciprofloxacin. Ceftriaxone in the treatment of typhoid fever was proved safe and effective in the present study

Key Words: *Cephalosporins, Ceftriaxone, Ciprofloxacin, Typhoid fever, quinolones.*

INTRODUCTION

Typhoid fever is an acute systemic disease resulting from infection with Salmonella typhi. The disease is unique to humans. The causative organism was first isolated by *Ebreth* in 1880. The disease has worldwide in distribution. The peak incidence of the disease is between the age of 15 and 35 years. It is rare in infants, especially below the age of 2 years. It is not commonly seen after 50 years. Males are more affected than females[18].

Since 1990 a multidrug resistant variety of Typhoid had been prevalent in many parts of India. The use of Quinolones in children has been prevalent. Ciprofloxacin used in children are not free from adverse effects. The resistant cases have a higher morbidity and require Cephalosporins.

Currently the III generation cephalosporins like ceftriaxone and cefotaxime are used in multi drug resistant typhoid fever. These drugs are more safe, bactericidal, less toxic, no toxicity on joints and cartilages. It can be used safely in children.

HISTORICAL ASPECT OF TYPHOID FEVER

This disease was named by *Louis* in 1829. The word typhoid is derived from '*typhoide'* which means 'disturbed mental condition' which is often present in this condition. Typhoid is an ancient disease and has been described by '*Hippocrates*' in his book '*Epidemic'*.

In 1880 *Eberth* obtained the causative organism Salmonella typosus, from the mesenteric gland. *Wright* in 1896, was the first to introduce prophylactic vaccination against typhoid. He injected heat-killed organisms to an Indian Medical Service Officer in three graduated doses. Later *Pfeiffer* and *Kelle* injected living organisms.

In 1896 - Widal introduced the serological means of diagnosis of the disease.

AETIOLOGY

Typhoid fever is caused by Salmonella typhi. It is a gram negative rod shaped organism about 3 micron in length and 0.5 micron in breadth. It has got flagella and is actively motile.

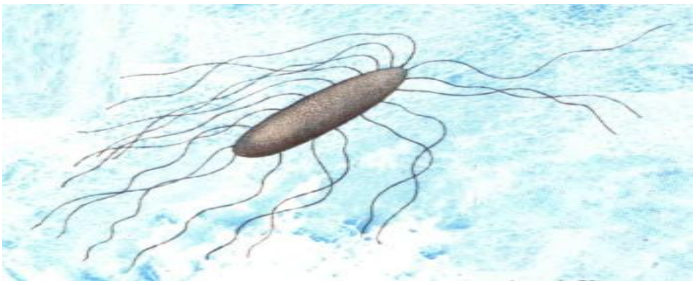


Diagram of Salmonella Showing Peritrichous flagella

Its optimum growth in seen at blood temperature. It is killed by boiling water and when exposed to a temperature of 60^0centigrade for 15 minutes.

OCCURRENCE

The organism S.typhi is found in the blood, Peyer's patches lymphoid follicles of the small intestine, faeces, mesenteric glands, lymph nodes, spleen, liver, gall bladder, kidney and urine.

MODE OF SPREAD

The infection spreads through infected food or drink. It is transmitted by the faeco oral route. The food may be contaminated from the following.

I. Carriers

Patients who continue to shed bacilli in faeces for 3 weeks to 3 months.

II.Flies:

Flies are important agents in the spread of infection by contaminating the articles of food.

III.Fomites :

Contract with articles used by the patient also aid in spread of infection.

IV.Water born :

Contaminated water is an important source for causing large epidemics.

Clinical Features of Typhoid Fever

The clinical features of typhoid fever are classically described by dividing the whole course of the disease into four weeks.

The First Week

The incubation period is usually 14 days, but may range from 5 - 20 days, and appears to be related to the dose of the infection. The disease is gradual in onset with malaise, loss of appetite and headache. The headache is usually in the frontal region. There is sore throat and the patient may have symptoms pertaining to respiratory system by way of nasal catarrh and cough. During: the first three days the patient is ambulatory but from third day on wards the symptoms become more severe. The temperature raises to step ladder fashion. The evening raise being greater by 0.5 to 1^0 F[6].

There is abdominal discomfort and slight distension. At this stage constipation is more common than diarrhoea and there may be vomiting. The tongue is dry and coated centrally. There are signs of bronchitis. The temperature continues to raise but pulse shows a relative bradycardia[7]. There is enlargement of liver. The spleen enlarges towards the end of the week[8].

Rose spots appear on the 7^{th} or 8^{th} day. They occur more commonly on the trunk, but they also are seen in other parts rarely. They are rose coloured, slightly raised and fade on pressure.

The Second Week

The temperature is raised and continuous. The patient becomes toxic there is mental apathy and he may become delirious. The relative bradycardia disappears towards the end of the week. The mouth and lips become dry and cracked and sticky mucus covers the mouth and tongue. The patient now develop diarrhoea and the typical peas cup stools may be seen. There is abdominal distension and spleen becomes larger.

The Third Week

In cases which recovered the temperature fall by about the fifteenth day. Toxaemia diminishes and appetite returns to normal. In unfavourable cases, the symptoms become more severe and the patient becomes profoundly toxic, the lapses into a stage of 'Coma Vigil' in which he is semi conscious, dehydrated, unaware of the surrounding and tremulous. Hence third week is the danger period for these unfavourable cases.

The third week is also the period of the most serious complications, intestinal hemorrahage and perforation of the bowel.

The fourth Week

The severe case runs a downhill course and dies. Uncomplicated cases after about 10 days of cessation of therapy, the attack is milder and less severe, complications are uncommon.

Typhoid Fever in Children

In children the disease may show more variable forms. It may be acute in onset, with vomitings, couvulsions and high fever. Diarrhoea may be present on the first day.

Some may show bronchopneumonia or lobar pneumonia. Meningism is often present. In some it may be very mild and pass off with vague symptoms. Haemorrhage and perforation are rare as the Payer's patches are not developed.

Typhoid Fever in the Aged

It is rare after the age of 40 years. Fever is slight but complications like hypostatic pneumonia and heart failure are common. Mortality is also high. In cases that recover convalescence is prolonged.

Typhoid Fever in Pregnancy

Abortion or premature delivery occurs in 60% of cases.

COMPLICATIONS

Gastrointestinal Tract

Superficial ulcers develop towards the end of first week on the anterior pillars of the fauces, soft palate and the pharyngeal wall. Intestinal haemorrhage occurs during third or fourth week. It is rare in children below the age of 12 years. The haemorrhage may be single or repeated. Repeated small haemorrhages are more dangerous than a single large bout.

Perforation of the bowel is the next dreadful complication of typhoid. It occurs in 2-4% of cases, usually in the third week. Like haemorrhage, this is also rare in children. The sites of perforation in order of frequency are lower part of ilium, caecum, appendix, colon, jejunum and sigmoid. The perforation is usually single, rarely multiple, perforation is hearalded by severe abdominal pain, starting in the right iliac fossa and spreading to the whole of the abdomen. There is fall of temperature even to subnormal level and signs and symptoms of peripheral failure.

Liver and Gall bladder

Acute cholecystitis may occur in the first week, when diagnosis becomes difficult. Rarely acute cholangitis, jaundice, perforation of gall bladder and liver abscess may take place.

Spleen

In rare cases spleenic abscess and spontaneous rupture of the spleen have been reported.

Respiratory System

Bronchopneumonia and lobar pneumonia may occur in the second or third week. Fibrinous pleurisy or pleural effusion may be seen. Rare complications are empyema, lung abscess, infarction and spontaneous pneumothorax.

Cardiovasuclar System

In severe cases acute myocardial failure or peripheral circulatory failure are common complications.

Central Nervous System

Meningism is of common occurrence in children right from the onset or sometimes late in the course of the disease. There are signs of meningeal irritation along with muscular twitchings and occasionally convulsions. Complete recovery occurs in the course of an year or two.

Ear: Temporary deafness occurs commonly in the course of the disease.

Clinical Diagnosis

In the past the question of diagnosis of typhoid fever was left to the laboratory. But in *Garron's* opinion the great majority of cases can be diagnosed clinically. The following clinical criteria should be applied.

a) Pyrexia of remittent type

b) Low pulse-temperature ratio

c) Characteristic toxaemia

d) Splenic enlargement

e) Eruption of rose-spots.

Treatment

1.Ciprofloxacin

There have been a shift in the preference of drugs from chloramphenicol to fluroquinolones especially ciprofloxacin. The fluoroquinalones are contraindicated in children because of its toxic effect on growing cartilage[24]. Changing trends in the antibiotic sensitivity pattern of S. typhi has been noticed recently.

2.Cephalosporins

Third generation cephalosporins are now considered as the first line drug against multi drug resistant typhoid fever.

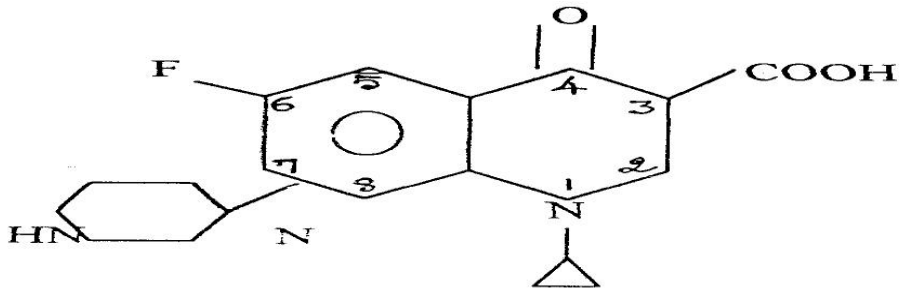
Ceftriaxone: It is a III generation cephalosporin, bactericidal, it prevents relapse and carrier state. Mechanism of action same as penicillin defervescence seen after 4-5 days. It can be safely used in children. It is the effective and safe drug in the treatment of typhoid fever.

Ciprofloxacin

Fluoroquinalones are quinolone antimicrobials having one or more fluorine substitutions. In 1990s compounds with additional fluoro and other substitutions have been developed.

Chemistry

2 – quinolones contain a carboxylic acid moiety in the 3 position of the basic ring structure. The newer fluoroquinolones also contain a fluorine substitution at position 6 and many of these compounds contain a piperazine moiety at position 7.



Mechanism of Action[23]

Potent inhibitor of nucleic acid synthesis. It blocks bacterial DNA synthesis by inhibiting DNA gyrase preventing the relaxation of super coiled DNA which in required for normal transcription and replication.

ADVERSE EFFECTS

Gastrointestinal: Nausea, vomiting, bad taste anorexia.

Central Nervous System: Dizziness, restlessness, anxiety and insomnia, convulsions.

Skin : hypersensitivity, photosensitivity swelling of lips, urticaria tendonitis and tendon rupture few cases have been reported.

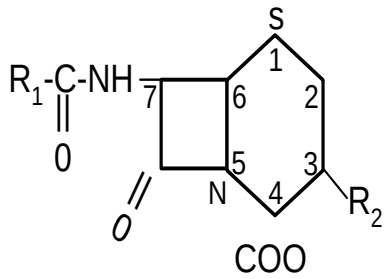
Bone: Arthralgias and joint swelling have developed in children receiving fluroquinolones. Therefore these drugs are not recommended in the prepubertal children.

Dosage: A dose of 500 – 750 mg b.d. for 10 days is recommended. Patients unable to take ovally are treated with 200 mg I.V. b.d in the beginning.

On an average fever subsidesin 4-5 days. Prevents carrier state due to cidal action. It is also used in treating carriers (750 mg b.d for 4-8 weeks).

CEPHALOSPORINS

Cephalosporins are semi synthetic antiobiotics derived from 'Cephalosporin-C' obtained from a fungus cephalospirium acremonium. The first source of cephalosporins, was isolated on 1948 by *Brotzu*. These are chemically related the pencillins. The nucleus consists of a Beta-lactum ring fused to dihydrothiazine ring (7 amino cephalosporamic acid). By addition of different side chains at position 7 of beta lactum ring (altering spectrum of activity) and position 3 of dihydro thiazine ring affecting pharmacokinetics, a large number of semisynthetic compounds have been produced.



CEPHEM NUCLEUS

All cephalosporins are bactericidal and have same mechanism of action as penicillin.

1. Bind to specific penicillin binding proteins. That serves as drug receptors on bacteria.
2. Inhibition of cell wall synthesis by blocking transpeptidation of peptidoglycan.
3. Activation of autolytic enzymes in the cell wall.

Adverse Effects

Side effects are local reactions including pain, induration and tenderness at injection site.

Side effects are: Rash, hypoprothrombanaemia and bleeding.

Dosage and administration

Preparation : 250 mg, 500 mg, 1 g vials are available.

Dose : 4 gms i.v. once a day for 2 days followed by 2gms per day till 2 days after fever subsides.

Place of Ceftriaxone in typhoid fever

Studies had been done. Typhoid fever responded very well and less side effects were noticed. It is safe in children and adults.

MATERIALS AND METHODS

The study was under taken in Typhoid fever patients attending Department of Medicine for the duration of 6 months.

Selection Criteria of the Patient

Patients were selected as per the exclusion and inclusion criteria.

Inclusion Criteria

- Patients aged between 15-40 years male and female were selected with history of continuous fever for more than 5 days duration with nausea, vomiting, abdominal discomfort.

- On examination raised body temperature, toxic look, coated tongue, hepatomegaly, splenomegaly were selected.

Exclusion Criteria

- X-ray chest was taken to rule out tuberculosis and other long diseases.
- Blood picture was taken to exclude malaria and fever due to other diseases.
- Typhoid cases complicated with perforation, peritonitis, meningitis, and encephalitis were excluded from the study.

After selection patients were divided into two groups.

Group – I-- 25 patientswere treated with Ceftriaxone parenterally 4gms iv once a day for 2 days followed by 2gms/day till 2 days after fever subsides and results were recorded.

Group - II -- 25 patients were treated with Ciprofloxacin 500-750mg b.d. for 10 days. Patients unable to take orally are treated and 200mg iv/bd and results were noted.

RESULTS

PATIENTS DEMOGRAPHIC DATA

In group-I-- The male, female ratio was 3:2.

In group-II-- The male, female ratio was 3:2.

Table – I Demographic date of patients Age and Sex distribution and duration of illness

Drug	Sex			Age in Years		Duration of illness in days
	N	M	F	Range between	Mean±SD	Mean±SD
Ceftriaxone-I	25	15	10	12-40	24.16±8.31	9.76±0.96
Ciprofloxacin-II	25	15	10	12-40	27.08±6.73	11.28±0.97
					P>0.05	P < 0.001

N = Number of patients M = Male F = Female

The duration of illness in Group I was mean 9.76 days and in Group II the duration was mean 11.28. The onset was insidious in all two groups.

Clinical Presentation

In Group - I All patients were presented with fever more than 102^0 F at the time of admission 16/25 (64%) of patients had headache, 22/25 (88%) were presented with abdominal discomfort and tenderness. 13/25(52) had vomiting, 6/25(24%) with diarrhoea, 20/25 (80%) were with splenomegaly and 10/25(40%) presented with hepatomegaly.

In Group - II all 25 patients were admitted with fever more than 102^0F temperature headache in 14/25(56%), abdominal discomfort and tenderness in 15/25 (56%), vomiting 16/25 (64%), diarrhoea 4/25 (16%), splenomegaly 10/25 (40%) and hepatomegaly 12/25(48%) were present.

Table – II Clinical presentation signs and symptoms

Drug	Fever >102^{0}F (%)	Head-ache (%)	Abdo-minal dis-comfort (%)	Vomiting (%)	Diarrohea (%)	Spleno-megaly (%)	Hepato-megaly (%)
Ceftriaxone-I	100	64	88	52	24	80	40
Ciprofloxacin-II	100	56	60	64	16	40	48
		P>0.05	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05

There were no significant differences observed among patients in the two groups with regard to age, sex, duration of fever before admission and clinical findings. (Table-I).

Days required for disappearance of signs and symptoms

The mean number of days for patients to become afebrile was significantly lowered in those receiving ceftriaxone (P < 0.001) than in those receiving ciprofloxacin (Table – III).

The mean number of days for regression of splenomegaly was significantly lowered in those receiving ceftriaxone (P < 0.001) than in those receiving ciprofloxacin (Table-III).

There is significant difference (P < 0.001) in the means of number of days for disappearance of abdominal discomfort and tenderness in those patients receiving ceftriaxone than ciprofloxacin (Table III).

Table – III Days required for disappearance of signs and symptoms

Sl. No.	Signs & Symptoms	Ceftriaxone-I	Ciprofloxacin-II	
1.	Afebrile	4.68±0.74	6.32±0.47	P<0.001
2.	Abdominal Distension	3.22±0.42	4.33±0.48	P<0.001
3.	Splenomegaly	4.20±0.41	5.12±0.61	P<0.001

Blood culture

Blood samples were sent for culture from all 25 patients in Ceftriaxone group, out of which only 8 blood samples had shown growth of S.Typhi. The blood culture was repeated after completion of therapy and found all 8 cases were sterile (Table – IV).

In Ciprofloxacin group 25 blood samples were sent in blood culture (S. Typhi) only 4 samples had shown growth of S. Typhoid. The blood culture was repeated after therapy and all four had shown sterile. (Table – IV)

Table – IV Blood Culture

Group	No. of samples sent	No. of samples +ve for Salmonella Typhi	After treatment Salmonella Typhi
Ceftriaxone-I	25	8	-ve
Ciprofloxacin-II	25	4	-ve

Widal Test

Widal test was done in both groups (group I and group II) before starting the therapy. The widal test was positive for both 'O' and 'H' in titre of more than 1:160 dilutions. After therapy the widal test was repeated and find significantly reduced titre of less than 1:160 dilution (0 and H) in both.

Table V Widal Test

Group	No. of samples sent	No. of samples +ve for Salmonella Typhi	After treatment O&H positive
Cefriaxone-I	25	25	-
Ciprofloxacin-II	25	25	11

Results of therapy

Clinical cure: In ceftriaxone group the clinical cure was seen in 25/25 (100%).

In ciprofloxacin group the clinical cure was seen in 14/25(56%). (table–vi)

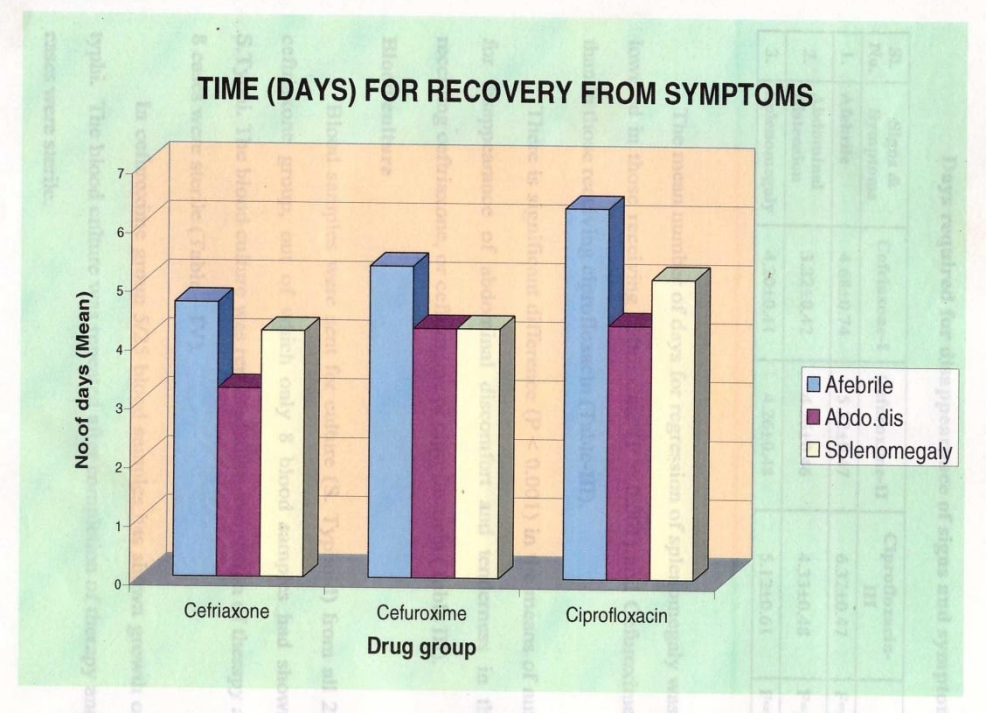
Table – VI Clinical Response

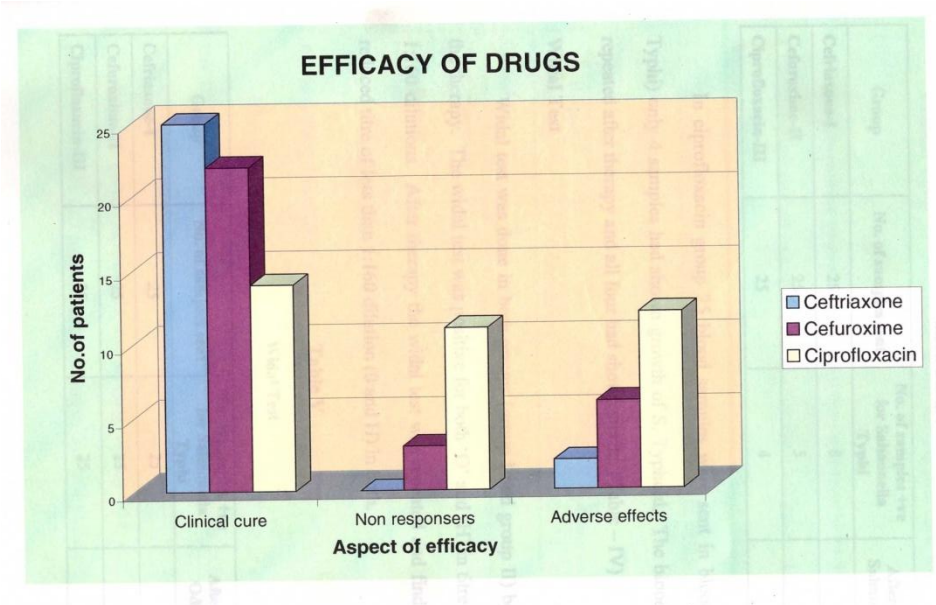
Group	Ceftriaxone-I	Ciprofloxacin-II
Clinical cure	25	14 P<0.001
Not responded to therapy	0	11 P<0.001
Adverse drug reactions	2	12 P<0.001

Adverse drug reactions:

The adverse effects were mild in ceftriaxone group, 2 patients had mild thrombophelbitis which was subsided within two days.

In ciprofloxacin group 12 patients had adverse effects like loss of appetite in 8 patients, insomnia in 3 patients and swelling of lips in 1 patient.


TIME (DAYS) FOR RECOVERY FROM SYMPTOMS
No.of days (Mean)
0
1
2
3
4
5
6
7
Cefriaxone
Cefuroxime
Ciprofloxacin
Drug group
Afebrile
Abdo.dis
Splenomegaly


EFFICACY OF DRUGS
No.of patients
0
5
10
15
20
25
Clinical cure
Non responsers
Adverse effects
Aspect of efficacy
Ceftriaxone
Cefuroxime
Ciprofloxacin

DISCUSSION

Ceftriaxone in the treatment of typhoid fever was proved safe and effective in the present study. Patients were recruited randomly as per our demographic data (Table-I) the mean age of ceftriaxone group was 24.6 years. The mean age of ciprofloxacin group was 27.08 years.

Males are frequently affected than females in the ratio of 3:2 in both the groups. The fever was mostly of continuous type and gradual onset. In ceftriaxone group the patients were responded and clinical cure was 25/25 (100%) cases.

The days required for the reduction of temperature to normal was even and significant ($P < 0.001$) in ceftriaxone than ciprofloxacin group. There was significant difference in the number of days required in disappearance of abdominal discomforts. ($P < 0.001$). There was significant difference ($P < 0.001$) in the number of days required in the regression of splenomegaly between ceftriaxone and ciprofloxacin group.

There was no serious adverse affects in ceftriaxone group and noted only two patients complained of thrombophlebitis.

Ceftriaxone is a third generation cephalosporin can be administered parenterally. It is safe in preschool children. It can be safely used in pediatric age group. The drug is well tolerated.

In the present study the clinical cure was 100% with Ceftriaxone parental therapy. The positive cultures for salmonella typhi were turned sterile after the completion of therapy. The stool and urine culture were negative. There were no relapses reported during the therapy and also after the follow up study period of four weeks. There was significant reduction in the widal agglutination titre after therapy.

In the present study all most all patients had shown the positive widal titre before treatment. The repeat widal test showed significant reduction in both ‘O’ and ‘H’ titre.

Fluroquinolones have offered affordable oral treatment option for adult patients. The safety of these agents in children is unsatisfactory, however recent reports of Salmonella resistant to ciprofloxacin and its adverse effects further reinforce the need for alternative therapy.

In ciprofloxacin group the clinical cure was only 56% (14/25) and large number of patients showed resistance to therapy (n=11) and adverse effects (n=12). The days required for the temperature differences was greater than ceftriaxone. The mean of temperature differences was significant ($P < 0.001$). The days required for the regression of splenomgaly was also showed significant disfference ($P < 0.001$) with ceftriaxone group.

SUMMARY AND CONCLUSION

Comparative study of 25 cases in each group of ceftriaxone and ciprofloxacin in the treatment of Typhoid fever was done. Ceftriaxone belongs to β-lactam group of drugs which are bactericidal, broad spectrum with less chance of development of resistance, with high therapeutic index and minimum adverse effects, taken for its effectiveness in the treatment of typhoid fever.

Ciprofloxacin is used in the treatment of typhoid fever. Its limitations in prepubertal children. Because of its adverse effects on growing

cartilages central nervous system and gastrointestinal system. Because of other factors we needed a more safer and effective drug.

Group I – Ceftriaxone 25 cases were treated, Group II– Ciprofloxacin 25 cases were treated with ciprofloxacin .

The common age group is 12-40 years. Males are affected more than females in the ratio of 3:2. All of 25 patients are from lower socio-economic group. Most of the patients are presented with continuous type of fever, abdominal discomfort, tenderness and splenomegaly. Investigations are sent before and after the starting of the specific therapy. Daily monitoring of temperature and other basic signs and symptoms are recorded for each group. The days required for the disappearance of signs and symptoms (1) temperature differences; (2) abdominal discomfort and (3) splenomegaly are summariged in the tables.

The number of patients responded clinically and not responded clinically are also explained.

The adverse effects in each group are also recorded and presented.

The present study has revealed that ceftriaxone parental therapy is more effective with less adverse effects.

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