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A Comparative Study of the Efficacy of 5 Days and 14 Days Ceftriaxone Therapy in Typhoid Fever in Children

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Abstract:
Background: *Typhoid fever is an acute multi-systemic infectious illness significantly contributing to considerable morbidity and mortality, particularly in developing Asian countries where about 80% of cases and deaths occur. In India also, it remains a serious health problem. A wide range of antibiotics ranging from Ampicillin, Co-trimoxable to Fluoroquinolones and third generation Cephalosporins have been used in the treatment of typhoid fever with variable success rates. In recent years, Ceftriaxone, a third generation Cephalosporin, has been increasingly used though the exact dosage and duration remains vague.*
Objectives: *The present study was carried out to study the clinical profile of children with typhoid fever and to compare the efficacy of 5 days with 14 days of Ceftriaxone therapy in children with typhoid fever.*
Methods : *This was an open randomized hospital based study, comparing Ceftriaxone given 100mg/kg/day IV for 5 days and 75mg/kg/day IV for 14 days in the treatment of uncomplicated typhoid fever in children, conducted in the Pediatric ward of Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur. 90 children with symptoms and signs of typhoid fever were enrolled in the study. The patients were randomly divided into 2 groups of 45 each. Patients aged between 3 to 12 yrs, with fever >4 days, diarrhoea, positive Typhidot test, a somatic O agglutinin of > 1:80 in Widal test, a positive blood culture for S.typhi were enrolled for the study. Patients with jaundice, gastro-intestinal hemorrhage or perforation, shock, known allergy to penicillin or cephalosporins & central nervous system involvement were excluded.*
Results: *The time to defervescence was comparable in both the groups. The outcome was classified as clinical cure in 44 patients (97.8%) in the 14 days group and in 38 patients (84.5%) in the 5 days group. Relapse was seen in 1 patient (2.2%) in the 14 days group and 7 patients (15.5%) relapsed in the 5 days group(p=0.026).*
Conclusion: L*ong course treatment with Ceftriaxone is significantly better than that of short course treatment with 5 days, although the latter is associated with short hospital stay, low cost and absence of side effects.*
Key words: *Typhoid fever, ceftriaxone, defervescence*

I. Introduction

Typhoid fever is a potentially fatal multisystem illness primarily caused by Salmonella enterica serovar typhi (S.typhi), a gram-negative bacterium and its classic presentation includes fever, malaise, diffuse abdominal pain and constipation.[1] The disease remains endemic in many areas of the developing world, causing over 21.6 million infections and over 2,00,000 deaths annually. The incidence is highest in South East Asia (over 100/100000 cases/year) with the highest burden of disease in children aged 2-15 yrs.[2] The annual typhoid rates (confirmed by blood culture) in recent studies from India, Pakistan and Indonesia range from 149 to as high as 573 cases per 100000 children.[3] Other regions contributing to global morbidity and mortality include Africa, Latin America, the Caribbean, and other parts of Asia.[2]

In the pre-antibiotic period, the disease burden was quite high with mortality reaching up to 15%, but with the universal introduction of Chloramphenicol in 1948, the mortality rate decreased to <1% and duration of fever also declined from 14-28 days to 3-5 days until the 1970's particularly in developing countries, when widespread resistance emerged.[4] Ampicillin and Trimethoprim-Sulfamethoxazole (TMP-SMZ) then became the treatments of choice. However, in the late 1980's, some S.typhi and S.paratyphi strains [multidrug resistant (MDR) S.typhi or S.paratyphi] developed simultaneous plasmid-mediated resistance to all these agents.[5] Fluoroquinolones then began to be recommended by most authorities for the treatment of typhoid fever, despite their potential toxicity and lack of data in children.[6,7] Initially they were greatly effective against susceptible organisms, yielding high cure rates. Unfortunately, resistance to first-generation fluoroquinolones developed and became widespread in many parts of Asia.[8,9,10]

In recent years, third-generation cephalosporins (ceftriaxone, cefixime, cefotaxime, cefoperazone) have been used in regions with high fluoroquinolone resistance rates, particularly in South Asia including India. They

are very safe for paediatric use with fever clearing rates averaging one week and treatment failure rates were 5-10 percent.[11,12] But most of them are administered parenterally and costly. Still, cephalosporins have remained an important therapeutic alternative for the therapy for typhoid fever, including multidrug resistant (MDR) typhoid in children with excellent primary cure rates.

The efficacy of third generation cephalosporin – Ceftriaxone, in typhoid fever is well documented.[13] But the precise duration of Ceftriaxone therapy in children with typhoid fever is not well established and varies from 3 to 14 days.[14,15]

Typhoid fever is also fairly prevalent in Manipur though the exact disease burden is not known and the present study was carried out to study the clinical profile of typhoid fever in children in a tertiary care centre in Manipur and compare the efficacy of a short course (5 days) with a long course (14 days) of Ceftriaxone therapy along with the determination of associated co-morbid conditions

II. Materials And Methods

The present study was conducted in 90 children with symptoms and signs of typhoid fever admitted in Pediatric ward, Regional Institute of Medical Sciences (RIMS) Hospital, imphal, Manipur (India) during the period from November 2010 to April 2012. The study was carried out after due approval by the Institutional Ethics Committee, RIMS,Imphal

Inclusion criteria comprised of children aged 3 to 12 yrs, having - fever >4 days, positive antibody IgM (Typhidot test), by a somatic O agglutinin of >1:80 in Widal test and a positive blood culture for S.typhi

Children with jaundice, gastro-intestinal(GI) hemorrhage or perforation, shock, known allergy to penicillin or cephalosporins central nervous system (CNS) involvement and not receiving consent from parents/legal guardians were excluded from the study.

The patients were randomly divided into 2 groups of 45 each.

A detailed history and clinical examination of all children were carried out after receiving informed consent from parents/legal guardians. The febrile child was evaluated through a series of tests and recordings : temperature from axilla for 3 minutes, complete hemogram (CHG), blood culture and sensitivity (C/S), blood for malarial parasite (MP), Typhidot test & Widal test, urine and stool routine examination (RE) & C/S. Liver function test (LFT), kidney function test (KFT), chest-X ray (CXR) and ultrasonography (USG) abdomen were performed as indicated.

Diagnosis of typhoid fever was based on detailed history, physical examination, a positive immunological test (Typhidot) **or** a somatic O agglutinin titer of > 1 : 80 in Widal test **or** a positive blood culture for S.typhi

After diagnosis, supportive & specific therapy (parenteral Ceftriaxone) was given to all the affected children.

Specific therapy – Intravenous (IV) Ceftriaxone -

1st group - 100mg/kg/day in two divided doses for 5 days

2nd group - 75mg/kg/day in two divided doses for 14 days.

The outcome of Ceftriaxone therapy was divided into three categories : cure, relapse & death.

Cure - The patient was considered clinically cured if there was resolution of all clinical symptoms and signs with negative blood culture for S.typhi or decreasing agglutination O titer at the end of treatment and if the patient remained clinically well during the follow-up period.

Relapse - A diagnosis of relapse was made if the patient responded to treatment clinically and then a recurrence of fever with blood culture positive for S.typhi or a rising somatic O agglutinin titer within 2 months following completion of therapy and with no evidence of exposure to suggest a new infection.

III. Results

A total of 5615 patients who were admitted in the Pediatric ward, RIMS,Hospital, Imphal during the study period of 18 months from November 2010 to April 2012. Out of the total admitted patients during the study period, 600 patients were found to be suffering from typhoid fever giving an incidence of 1.06 per 1000 children.

The age of the patients ranged from 3-12 years and the mean age was 8.1±2.7 years. Maximum number of cases belonged to the age group 6-12 years comprising of 74 (82.2%) cases. There were 58(64.4%) male patients and 32(35.5%) female patients with male to female ratio of 1.8:1.

There were 17(18.8%) cases from lower socio-economic group; 36(40%), 34(37.8%) and 3(3.4%) belonged to lower socio-economic, upper lower, lower middle and upper middle socio-economic groups respectively.

There was variation in the number of cases in different months with the maximum numbers of cases observed during May to September.

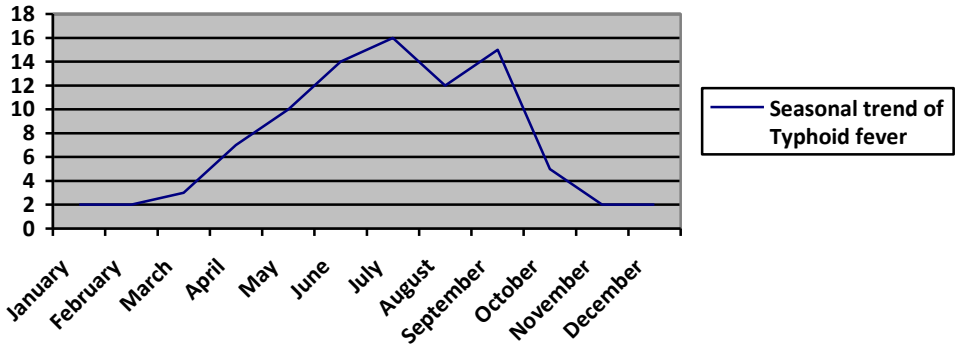

Fig :- 1. Seasonal trend of Typhoid fever

There were 63(70%) cases belonging to Hindu religion; 18(20%) cases and 9(10%) cases belonged to Muslim and Christian religions, respectively.

The mean duration of illness in children with typhoid fever who were treated with long course Ceftriaxone therapy was 10.6±2.4 days and that in children treated with short course Ceftriaxone therapy was 10.2±2.6 days. There was no significant variation in duration of illness (P=0.44).

Blood culture was positive only in 2(4.4%) patients treated with the long course Ceftriaxone therapy whereas 3(6.7%) children were positive by blood culture among those receiving short course.

Of the various clinical signs and symptoms, the most common presenting feature was fever (100%) in each group followed by coated tongue (84.4% in children allotted to long course and 77.8% in children given short course), hepatomegaly, pain abdomen, diarrhoea, constipation, cough, vomiting and rashes respectively (Table - 1) with no statistically significant difference between the two groups (P = 0.45).

Table :- 1. Clinical profile of children with typhoid fever with respect to course of Ceftriaxone therapy

Clinical feature	Long course No.(%)	Short course No.(%)
Fever	45 (100)	45 (100)
Cough	15 (33.3)	10 (22.2)
Rashes	3 (6.67)	2 (4.4)
Coated tongue	38 (84.4)	35 (77.8)
Pain abdomen	20 (44.4)	23 (51.1)
Vomiting	10 (22.2)	2 (4.4)
Constipation	15 (33.3)	12 (26.7)
Diarrhea	18 (40)	13 (28.9)
Hepatomegaly	20 (44.4)	28 (62.2)
Splenomegaly	15 (33.3)	15 (33.3)

[χ^2 = 8.840; df = 9; P = 0.45]

The co-morbid conditions that were seen in the affected children were hepatitis, anemia, pneumonia, cholecystitis, arthritis, encephalopathy and meningitis, respectively (Table - 2). Here also, there was no significant variation between the two groups.

Table :- 2. Comparison of associated co-morbid conditions among children with typhoid fever on long and short course Ceftriaxone therapy

Co-morbid conditions	Long course No. (%)	Short course No.(%)
Pneumonia	8(17.8)	7(15.6)
Cholecystitis	8(17.8)	7(15.6)
Meningitis	1(2.2)	1(2.2)
Arthritis	4(8.8)	5(11.1)
Anemia	10(22.2)	12(26.7)
Hepatitis	14(31.1)	15(33.3)
Encephalopathy	2(4.4)	2(4.4)

[χ^2 = 0.399; df = 5; P = 0.995]

In the present study, a total of 54.4 % of the patients were positive by Typhidot test, 44% by Widal test and 5.5% were positive by blood culture (Table – 3)

Table :- 3. Characteristics of specific investigations of children with typhoid fever

Investigation	Long course No.(%)	Short course No.(%)	Total No.(%)
Typhidot (+)	25(55.6)	24(53.3)	49(54.4)
Widal test (+)	20(44.4)	20(44.4)	40(44.3)
Blood culture (+)	2(4.4)	3(6.7)	5.(5.6)

Other biochemical and laboratory work up of the patients in either group were found to be comparable with no significant differences.

Table :- 4. Characteristics of treatment outcome of typhoid fever with respect to course

Characteristics	Long course	Short course	X^2 or t-value	p-value
Time to defervescence in days (Mean±SD)	3.82 ± 0.86	3.93 ± 1.07	0.541 t-value	0.590
Outcome			3.873 X^2	0.026
Cured(%)	44(97.8)	38(84.5)		
Relapse(%)	1(2.2)	7(15.5)		

*χ^2 is applied in case of data expressed in %
**t-test is applied in case of data expressed in Mean±SD

The mean time to defervescence in children with typhoid fever who received long course Ceftriaxone therapy was 3.82 ± 0.86 days and 3.93 ±1.07 days in those receiving short course Ceftriaxone therapy (P=0.59). However, the cure rate among children who received long course therapy was 97.8% as compared to 84.5% among children who received short course Ceftriaxone therapy (Table – 4). Only one patient who received long course Ceftriaxone treatment relapsed whereas 7 patients in the short course Ceftriaxone therapy suffered relapse, giving a relapse rate of 15.5% [as against 2.2% in the long course Ceftriaxone therapy group (P=0.026)].

IV. Discussion

In the present study, it is observed that enteric fever is still quite prevalent throughout the year, but maximal cases occurring between May to September (Fig-1) with an incidence of 1.06 per 1000 admissions. The maximum number of cases were seen in the aged group of 6 – 12 years with male preponderance (M : F = 1.8:1) underlining the fact that it is a disease of school going children. This is comparable with Rajiv Kumar *et al*[16] who had also found a male to female ratio of 1.85:1, but he observed two peaks of incidence - highest incidence of disease occurring in the 2-5 years age group and second highest peak in the 7-10 years age group. Raman *et al*[17] had also reported the average age of typhoid infection as 5.6 years and male to female ratio of 3:2. The majority of the cases in our study were from the indigenous Meitei Hindu community followed by Muslims and Christians. This appeared to have no scientific significance and may be explained by the fact that majority of the local population of Imphal Valley are Hindus. It was also found that maximum number of cases were from upper lower and lower middle socio-economic groups[18] emphasizing that typhoid fever is a disease of poverty as it is often associated with inadequate sanitation facilities and unsafe water supplies. Interestingly all the families of affected children in our study reported using either tap or potable water supply for domestic consumption; also majority of the families had access to sanitary latrines.

Fever was the commonest presenting symptom and the mean duration of fever was 10 days (range 8 – 12 days) with no variation observed in fever duration in both groups (Table – 1). The two groups were also comparable in their clinical characteristics, duration, severity of illness at admission and other co-morbid conditions (Table-2). In the present study, 54% of patients were positive by Typhidot test, 44% positive by Widal test and 5.5% positive by blood culture (Table – 3) which correlates with the study of Narayanappa *et al* [19] who also found a higher sensitivity for Typhidot as compared to Widal test in the diagnosis of enteric fever in children. The relatively low sensitivity of blood culture in diagnosing typhoid fever is understandable in the wake of widespread antibiotic use in India and technical difficulties in obtaining large volume of blood for blood culture in children. Although bone marrow cultures significantly increase the yield of Salmonella, they are invasive, difficult to obtain and take at least 2-3 weeks for the results to come.

There were no substantial differences in clinical and laboratory parameters between the study groups. Ceftriaxone used in our study was well tolerated without any untoward side effects observed among the study subjects. But the relapse rate in the short course Ceftriaxone therapy was significant [15.5% as against 2.2% in the long course group (p=0.026)] (Table-4). This is slightly higher but comparable with Bhutta ZA *et al* [20] where the relapse rate was 14% in the short term Ceftriaxone therapy. The time to defervescence was comparable in both groups - 3.82 ± 0.86 days in the long course as against - 3.93 ± 1.07 in the short course

(Table-4). This was comparable with the study of Bhuta ZA *et al*[20] where he observed that time to defervescence was comparable between two groups of children with MDR typhoid (3.7 vs 4.1, though p-value was not significant). Girgis *et al*[21] had also reported a cure rate of 95% among children with MDR typhoid (who were given a 5-day course of ceftriaxone) with time to defervescence of 3.9 days, But the present study's defervescence time is considerably shorter than the observed pattern of defervescence for typhoid in other studies.[20,22]

Our data suggest that despite comparable bacteriological and clinical cure rates, a 5-day course with Ceftriaxone was associated with relatively higher rate of relapse in children with typhoid fever, in comparison with a 14-day course of treatment. This data is at variance with information from other studies of short course therapy with Ceftriaxone for adults and children with typhoid.[22,23] However despite adequate documentation of a cure, few of the studies had inadequate follow-up periods and did not address the issue of relapse. In Vietnam, where there was an overall 63% incidence of MDR typhoid, Smith *et al*[24] observed a 28% primary treatment failure for a 3-day course of Ceftriaxone therapy. It is thus possible that these differences in response to therapy may represent differences in the virulence and antibiotic responsiveness of different strains of S.typhi. It is therefore imperative that therapeutic strategies for treating typhoid in children must take local epidemiological patterns and strain specifications into account.

V. Conclusion

The present study demonstrates comparable efficacy of Ceftriaxone 100mg/kg/day in a single or two divided doses for 5 days to Ceftriaxone 75mg/kg/day in one or two divided doses for 14 days with no significant side effects observed in either group during the course of therapy. Ceftriaxone administered over a period of 5 days had the advantage of short hospital stay, rapid response, low cost and absence of serious side effects. However, a higher relapse rate was seen in the short course group as compared to the long course group, suggesting that a short course therapy is inadequate in the treatment of typhoid fever. Although the clinical response and bacteriological clearance rates during the period of hospitalization were comparable for both groups, it is possible that a 5-day course may be insufficient in clearing S.typhi from the macrophages within the reticuloendothelial system, thereby provoking a relapse. Therefore considerable caution should be emphasized in treating typhoid fever with parenteral Ceftriaxone for 5 days. It is uncertain if an intermediate course of therapy, one between 5 and 14 days, would be adequate for treating typhoid fever, and further studies are needed to explore this issue.

However, it is also realized that though the current results are encouraging, the number of patients in the present study was small and all the patients were uncomplicated cases of typhoid fever. Therefore, whether Ceftriaxone 75mg/kg/day for 14 days is superior, equal or inferior to Ceftriaxone 100mg/kg/day for 5 days in cure, relapse or carrier rates may be determined by future randomized comparative studies.

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