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**An Evaluation of the Duration of Injection Ceftriaxone Treatment in Children with Enteric Fever in Culture Positive Cases: A Study in a Specialized Shishu (Children) Hospital & ICH, Mirpur, Dhaka, Bangladesh**

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| **Abstract** |  | **Original Research Article** |

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| It was an observational study. The study was conducted in the Department of Paediatrics, Dr. Mr. Khan Shishu(children) Hospital and ICH, Mirpur-2, Dhaka over a period of 6 months from July 2014 to December 2014.A total of 30 hospitalized children with clinical/or laboratory diagnosis of enteric fever admitted in the above mention place were the study population. The aim of this study was to evaluate the duration of injection ceftriaxone treatment in children with enteric fever in culture positive cases. .A total of 30 hospitalized children with clinical/or laboratory diagnosis of enteric fever admitted in the above mention place were selected as the study subjects. In our study, most of the study subjects were more than 8 years of age and mean age was (8.4 ± 2.8) in the range of 2-12 years. Females were dominating the sex distribution which are 19(63%) and most of the study subjects were in middle class status which are 16(53.3%) in the socio-economic distribution. Fever were the common symptoms of all study participants and continues 5-6 days most of the participants 19(63.3%). In addition, Headache were the another most common symptoms 7(23.3) in the study subjects. Signs were Hepatomegaly, Splenomegaly and Coated tongue 53.3 %, 43.3% and 93.3% respectively. Most of the study participants’ 17(56.7%) weight at admission were less than 20 kg. Weight was steady at admission and after 1 month, therefore the weight began to increase gradually and brought 21.8 ± 4.9 kg after 2 months and 21.9 ± 5.1kg after 3 months, which were statistically significant. The mean temperature before treatment was 102.1 ± 2 0F which decreased about 97.9 ± 10F after 1 month and increase to after 2 months (98 0F) thereafter the temperature experienced a steady after 3 months of treatment (98 0F). The difference of temperature at each level of evaluation throughout the observation period was statistically significant (p < 0.001). The study findings depicts that 50% of the patients had a history of duration of treatment between 6 – 7 days, 20% between 8 – 9 days and remaining 30% 10 days. The mean duration of treatment was 8.1 ± 1.4 days. Sixty percent of the patients had defervescence between 3 – 5 days after treatment with injection ceftriaxone and 40% between 6 – 9 days. The mean duration of defervescence was 5.3 ± 1.5 days and all children recovered completely after treatment and none had clinical relapse. In the conclusion, we can say that the effectiveness of injection ceftriaxone responded to ceftriaxone therapy with no treatment failure. Majority of case had fever clearance time less than 6 days. No case was reported as relapse on follow up.  **Keywords:**Injection ceftriaxone, Enteric fever, Treatment, Culture positive case. |

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**INTRODUCTION**

Enteric fever is a common term to encompass two similar clinical illnesses, caused by different serotypes of the bacterium Salmonella enterica [1]. Typhoid fever is generally more common and more severe, but recent reports suggest that the relative frequency of paratyphoid fever may be increasing [[2](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0083#CD004530-bbs2-0083)-[8](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0114#CD004530-bbs2-0114)]. In the year 2000, there were an estimated 21.6 million cases of typhoid fever, with 210,000 deaths and 5.4 million cases of paratyphoid fever [[9](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0121#CD004530-bbs2-0121), [10](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0092#CD004530-bbs2-0092)].The symptoms of enteric fever are generally non-specific and can vary among different children [[11](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0124#CD004530-bbs2-0124)]. Common symptoms include fever, headache and gastrointestinal complaints; such as diarrhoea, constipation, abdominal pain, nausea and vomiting or loss of appetite [[12](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0110#CD004530-bbs2-0110), [13](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0129#CD004530-bbs2-0129)]. Severe disease occurs in 10 to15% of children and complications such as; intestinal perforation, intestinal bleeding, shock, pancreatitis, pneumonia, myocarditis, meningitis or psychosis can occur, typically after the illness has lasted more than two weeks [[11](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0124#CD004530-bbs2-0124)]. The bacteria may be shed in the faeces during the acute illness, during convalescence and occasionally for prolonged periods when the patient is labelled a 'chronic carrier' [[14](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0078#CD004530-bbs2-0078)]. Infection occurs when food or water contaminated with faecesharbouring the bacteria are ingested. The organisms then penetrate the intestinal lining, multiply in lymphoid tissues and are released into the blood stream from where they spread throughout the body to various organs; most commonly the liver, spleen, bone marrow and gall bladder [[15](file:///C:\Users\USER\AppData\Local\Temp\Temp1_redissertation%20(2).zip\int3.htm#CD004530-bbs2-0112#CD004530-bbs2-0112)]. Ceftriaxone is a third-generation cephalosporin. In common with most of the other third generation agents, it has an aminothiazolyl substitution at the R1 position of the β-lactam ring. Since the mid-1980s when ceftriaxone was first introduced, the drug has been used extensively because of its improved stability against β lactamases, efficacy in a broad range of infections and its pharmacokinetic and tolerability profile [16]. Pharmacokinetic properties of ceftriaxone, such as sustained tissue drug levels over 24 hours after a single injection; good penetration of the antibiotic into cells; significant biliary excretion as active unchanged compound and high potency against S. typhi, should make it possible to significantly shorten the treatment of enteric fever. Although the efficacy of ceftriaxone in enteric fever is well documented, the precise duration of ceftriaxone therapy in children with enteric fever is not established and varies from 3 to 14 days [17]. This has been well discussed by Tatli *et al*. [18] in a prospective randomized study, ceftriaxone used for treatment of 72 children who had bacteriologically confirmed enteric fever. Ceftriaxone was given at a dose of 75 mg/kg per day (maximally 2 g/day) intravenously, in two doses until defervescence and continued 5 days after that time. Mean defervescence time was in 5.4 days in the ceftriaxone group. Clinical cure without complications was achieved in all patients and no patient relapsed. They suggested that a flexible-duration of ceftriaxone therapy given until defervescence time, followed by an additional 5 days of therapy is a reasonable treatment in children with enteric fever [19]. Other study has shown ceftriaxone was the commonly prescribed antibiotic and duration of treatment ranged from 10 to 14 days. Nalidixic acid-resistant S typhi was seen in 56%. The mean duration of hospitalisation was 6.94 days. In light of these findings, ceftriaxone showed a safe and effective alternative therapy to first line therapies for the treatment of enteric fever in children. In addition, ceftriaxone shortens duration of fever substantially, thus reducing the hospital stay [20]. In our country, so far, no study has been carried out to find out the defervescence time as well as total duration of treatment in enteric fever with ceftriaxone. The aim of this work is, therefore, to study the duration of treatment of culture positive enteric fever with injection ceftriaxone in a tertiary care hospital. Enteric fever is a global health problem; risk is highest among children living in poverty in the developing world like Bangladesh where water and sanitation services may be inadequate and continues to be a major health problem despite the use of antibiotics and the development of newer antibacterial drugs. The highest incidence has been reported in children between 5 and 10 years of ages. For improved treatments of enteric fever and multidrug resistant S*. typhi*in particular, attention has been focused on ceftriaxone because of excellent properties. This highly active drug reduces the duration of treatment from the traditional 14 days that is necessary first line antibiotics. So there is still lack of information about the actual duration of treatment of culture positive enteric fever in the different area of Bangladesh. This study will help us to know about the duration of treatment with injection ceftriaxone in culture positive enteric fever cases in the tertiary level hospital.

**Objectives**

**General objective**

* To evaluate the duration of injection ceftriaxone treatment in children with culture positive enteric fever.

**Specific objectives**

* To find out the fever clearance time treated by injection ceftriaxone.
* To asses presenting clinical signs & symptoms in enteric fever children.

**MATERIALS AND METHODS**

It was an observational study. The study was conducted in the Department of Paediatrics*, Dr. Mr. Khan Shishu(children) Hospital and ICH*, Mirpur-2, Dhaka over a period of 6 months from July to December, 2014.A total of 30 hospitalized children with clinical/or laboratory diagnosis of enteric fever admitted in the above mention place were the study population. But due to time constraint as well as lack of number of patients, only 30 cases were included in the study. This study was done over 6 months and 30 cases were included in the study. All suspected cases of enteric fever after admission in hospital, detailed history was taken and clinical examination was done. Then investigations were sent like CBC, blood culture, urine R/E. On the basis of clinical suspicion of enteric fever empirical treatment was started with I/V injection ceftriaxone from the first day of hospitalization. Dose of drug was 75 mg/kg/day max. 2g. only the culture positive enteric fever cases were included in the study and treatment was given 3 days more from the day of defervesenceof fever. Full treatment was given in the hospital. The duration was about 7-10 days. Then the patients were discharged with advice for follow up monthly for 3 months and to visit any time if fever comes.

**Inclusion Criteria**

Patients with following characteristics were included in the study. Patients aged 2 to 12 years of age**,** Patients of either sex**,** Fever ≥ 38°C for ≥ 4 days**,** Culture positive

**Exclusion criteria**

Patients with following characteristics were excluded from the study: Culture-negative, Evidence of severe disease, Prior use of antibiotics within one week of hospital admission.

**RESULTS**

The present study was conducted on 30 paediatric patients up to the age of 12 years to evaluate the duration of treatment of culture positive enteric fever with injection ceftriaxone. The findings of the study derived from data analysis are presented below.

**Table-1: Distribution of patients by age, sex and Socio-economic class (n = 30)**

|  |  |  |
| --- | --- | --- |
| Age | Frequency | Percentage |
| ≤5 years | 06 | 20.0 |
| 6 – 8 years | 08 | 26.6 |
| >8 years | 16 | 53.3 |
| Mean Age | (8.4 ± 2.8) | |
| Range | (2 – 12) years | |
| Sex |  |  |
| Male | 11 | 37 |
| Female | 19 | 63 |
| Socio-economic status |  |  |
| Poor | 7 | 23.3 |
| Middle Class | 16 | 53.3 |
| Upper Class | 7 | 23.3 |

**Table-2: Distribution of patients by signs and symptoms (n = 30)**

|  |  |  |
| --- | --- | --- |
| Signs & Symptoms | Frequency | Percentage |
| Symptoms | | |
| Fever | 30 | 100.0 |
| Duration of fever  5 – 6 days  7 – 8 days | 19  11 | 63.3  36.7 |
| Loose stools | 02 | 6.7 |
| Headache | 07 | 23.3 |
| Anorexia | 02 | 6.7 |
| Abdominal pain | 01 | 3.3 |
| Signs | | |
| Hepatomegaly | 16 | 53.3 |
| Splenomegaly | 13 | 43.3 |
| Coated tongue | 28 | 93.3 |

**Table-3: Distribution of patients by weight at admission (n = 30)**

|  |  |  |
| --- | --- | --- |
| Weight(kg) | Frequency | Percentage |
| ≤20 | 17 | 56.7 |
| 20– 25 | 07 | 23.3 |
| >25 | 06 | 20.0 |

**Table-4: Weight and Temperature at different time interval (n = 30)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean | Standard deviation | p-value |
| Weight (kg) | | |  |
| At admission | 21.6 | 4.9 | <0.001 |
| After 1 month | 21.6 | 4.9 |
| After 2 months | 21.8 | 4.9 |
| After 3 months | 21.9 | 5.1 |
| Temperature | | |  |
| At admission | 102.1 | 2.0 | <0.001 |
| After 1 month | 97.9 | 1.0 |
| After 2 month | 98.0 | 00 |
| After 3 month | 98.0 | 00 |

**Table-5: Distribution of patients by outcome (n = 30)**

|  |  |  |
| --- | --- | --- |
| Outcome | Frequency (%) | Mean ± SD |
| Duration of treatment  6 – 7 days  8 – 9 days  10 days | 15(50.0)  6(20.0)  9(30.0) | 8.1 ± 1.4 |
| Day of defervescence  3 – 5 days  6 – 9 days | 18(60.0)  12(40.0) | 5.3 ± 1.5 |
| Recovery | 30((100.0) |  |

**DISCUSSION**

Salmonella typhi infection remains a serious problem in developing countries. With an estimation of 12.5-16.6 million cases each year and 600 000 deaths, typhoid fever continues to be a major cause of morbidity and mortality in tropical countries, especially among children [21, 22]. However, in more affluent regions of the world, proper sanitation has successfully diminished the infections with S.typhi. Enteric fever in children in the first 2 years of life exhibits certain differences from the clinical course in adults [23]. The results of this treatment trial confirm those of other studies which used ceftriaxone in cases of enteric fever [24, 25] i.e., this antibiotic achieved satisfactory clinical and bacteriologic responses. In our study, 20% of patients were 5 years or less than 5 years, 26.6% between 6 – 8 years and 53.3% more than 8 years. Previous studies have also shown that about 22% to 30% of enteric fever cases in children upto 15 yrs of age are of less than 5 yrs of age [26, 5]. Another study in Northern India also showed that the majority of cases occurred in children aged 5 to 12 years, 22.8% of cases were in children up to 5 years of age and 6% to 21 % were in less than 2 years of age [27]. Almost similar study done by Sinha *et al*. [28] showed 24% children were aged less than 5 years. In our study, among 30 culture positive enteric fever cases 37% were male and 63% were female. This finding was closely similar with Deshmukh *et al*. [29] who reported 31% male and 69% female. Another study done by Butler *et al*. [30] also showed that infection rate is higher in female, perhaps reflecting greater exposure of female to contaminated food and water outside the home.

Enteric fever may be particularly difficult to diagnose in infants, as Secmeer *et al.* in 1995 have reported, 10 patients in their series having mild illness characterized by non-specific symptoms such as fever and cough. In our study fever was the commonest presentation in all of the patients. The other symptoms were headache in 23.3%, loose stools in 6.7%, anorexia in 6.7% and abdominal pain in 3.3% of patients. Hepatomegaly was detected in 53.3%, splenomegaly in 43.3% and coated tongue in 93.3% of patients. These findings were almost similar to those of a previous study by Threlfall *et al.* [31], which showed fever in 95% of patients, headache in 22.7%, loose stool in 9%, anorexia in 5.1% and abdominal pain in 3.9%. In another Retrospective analysis of 52 cases of enteric fever in a tertiary care hospital in Dhaka city conducted by Mutanabbi *et al*. observed that hepatomegaly and splenomegaly were the major physical findings in their study. Few other studies have also found these to be inconsistent features of enteric fever. Rafiq *et al.* in [32] noted that fever, vomiting, abdominal pain, loss of appetite; diarrhea and cough were the predominant symptoms. Hepatomegaly was detected in 9 (9%), splenomegaly in 13 (13%) patients. Yaramis *et al*. [33] reported in their study hepatomegaly was higher than splenomegaly (71% vs.52%). Long *et al*. [34] reported in their series hepatomegaly was almost twice as frequent as splenomegaly. Threlfall *et al.* [31] also reported in a large series in children with enteric fever, 32% had elevated liver enzymes, while only 9% had hepatomegaly with or without splenomegaly. In another study Cooke *et al*. [35] found 17% encephalopathy, 73% hepatitis, 4% pneumonia, 4% gastrointestinal bleeding; but we did not find similar features. Based on the results of the present study, we observedmean weight of children was almost steady at admission and after treatment of 1 month (21.6 ± 4.9 kg at admission and 21.6 ± 4.9 kg after 1 month) and began to increase gradually and brought 21.8 ± 4.9 kg after 2 months and 21.9 ± 5.1kg after 3 months (p < 0.001). In agreement with the present findings, several studies showed that mean weight increased throughout the different time points [22, 21]. In another study conducted by Threlfall *et al*. in [31] also observed improved weight (as was found in the present study), indicating there was a significant (p < 0.001). Our study showed that mean temperature before treatment was 102.1 ± 2 0F which decreased about 97.9 ± 10F after 1 month and increase to after 2 months thereafter the temperature experienced a steady after 3 months of treatment (98 0F). This findings conducted in others had almost similar results to ours [36, 37].

The present observational study revealed that the effectiveness of injection ceftriaxone in term of fever clearance and treatment failure rate in children with enteric fever. All 30 enrolled cases responded to ceftriaxone therapy with no treatment failure. Majority of case had fever clearance time less than 6 days. No case was reported as relapse on follow up. The same was stated in other study conducted by Madhulika *et al*. [38]. Several studies done in India and other part of world also showed considerable variation in fever clearance time for ceftriaxone for enteric fever in children. The mean fever clearance time with ceftriaxone observed in our study was 5.3 days as against 6.1 days in literature [11]. In another study by Kumar *et al*. from Delhi in year 2007, 93 blood culture proven typhoid cases in children were randomized to ofloxacin treatment group and ceftriaxone group. Mean defervescence time with ceftriaxone and ofloxacin was 4.25 and 4.96 days respectively. A retrospective analysis of 135 typhoid cases was conducted in Kuwait in 2007 by Dimitrov *et al*. total 108 children were treated with Ceftriaxone and mean defervescence time was 6.3 days. A retrospective chart review of all cases of culture proven enteric fever was carried out at a tertiary care private hospital in Mumbai over the period January 2003 to September 2005 by Jog *et al*. [39] total 72 children were treated with ceftriaxone and mean defervescence time 4.2 days was noted. The mean defervescence time in our study is similar to the finding in various previously done studies. In year 1992, Gulati *S et al*. randomized fifteen cultures proven typhoid cases in three groups (ceftriaxone, cefotaxim, and ciprofloxacin) and noticed mean fever clearance time 5.1 days in ceftriaxone group. In another trial Tatil *et al*. in year 2003 Ceftriaxone was given in 72 bacteriological confirmed typhoid fever children resulted in mean fever clearance time of 5.4 days. However, Ceftriaxone for treating typhoid fever will be useful for patients in whom a shorter course of injectable-drug therapy is preferable. Further study should be conducted to validate the findings of the present study.

**Limitations of the study**

Sample size of our study was very small that can’t be generalized in the whole country. In addition, we conducted this study in a hospital, so that this finding can’t reflect the scenario in the whole country.

**CONCLUSION AND RECOMMENDATIONS**

In the conclusion, we can say that the effectiveness of injection ceftriaxone responded to ceftriaxone therapy with no treatment failure. Majority of case had fever clearance time less than 6 days. So, injection ceftriaxone treatment might be a good solution in children with enteric fever in culture positive cases. Our study was conducted in a single centre with sample size small. We are recommending multi-centre study with large sample size for a better outcome.

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