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Potent Antibiotic to Treat Typhoid Fever in Patients of Pediatric Age-group

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Authors' contributions

This work was result of joint effort by all authors. Author AN did the study conception, data acquisition and analysis and drafting of the manuscript. Author AA managed the data acquisition and interpretation, revision, and final approval. Author GH did the counseling of patients, got consent from parents/guardians of patients, and data acquisition and analysis. All authors independently read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work.

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Original Research Article

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ABSTRACT

Aims: To evaluate the safety and effectiveness of Cefixime and chloramphenicol taken orally in the treatment of typhoid fever in pediatric patients.
Study Design: Randomized Clinical Trial.
Place and Duration of Study: Department of Pediatric Medicine, DHQ Teaching Hospital, Sahiwal and Sahiwal Medical College, Sahiwal (Pakistan) from May to October 2017.
Methodology: We included 60 patients diagnosed with typhoid fever confirmed by blood culture in this study and divided them into two groups. Group A received Cefixime while Group B was treated with Chloramphenicol. All patients were treated on indoor basis after admission to the ward and defervescence period was recorded in days for every patient. Non-responders were treated with alternative antibiotics in time as advised by the ethical review committee.
Results: Among group A patients, Cefixime cured 28 out of 30 patients successfully with an efficacy of 93.3%, while in Group B, chloramphenicol was successful in treating 13 out of 30

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patients with a cure rate of 43.3% (P value was 0.01). Overall in this study 45 patients were treated with Cefixime, of which 43 were cured successfully (95.5%) with a P value of 0.005.
Conclusion: Cefixime is a superior choice at present times in this region of Pakistan for the treatment of typhoid fever.

Keywords: Typhoid fever; Salmonella typhi; cephalosporin; Cefixime; chloramphenicol.

ABBREVIATIONS

CSP : Cephalosporin
DHQ : District Headquarters (Hospital)
GCS : Glasgow Coma Scale (Score)
MDR : Multidrug Resistant
OPD : Out Patient Department or Outdoor Patient Unit
Typhoid: Typhoid Fever, as Infection of Salmonella typhi
WHO : World Health Organization

1. INTRODUCTION

The incidence of typhoid fever as per estimates of World Health Organization (WHO) is around 12.5 million cases around the globe every year [1]. However, the incidence in developing countries is much higher at a figure of 50 per 1000 every year [1]. Data of pediatric ward of District Headquarters (DHQ) hospital in Sahiwal (a district in central Punjab, Pakistan) shows that out of 1180 indoor admissions during 2016 and 2017, there were 27 patients diagnosed with typhoid fever. This unpublished data shows that typhoid fever (hereinafter referred to as typhoid) was the cause of 2.29% admissions in pediatric indoor while the figures for patients treated on outdoor (OPD) basis are much higher.

Chloramphenicol has been a drug of choice in the treatment of typhoid but in 1972 there were reports of resistant strains in Mexico [2,3]. During 1990s, UK data states that around one-fifth of Salmonella typhi strains were resistant to chloramphenicol [4]. In the first decade of 21st century, some strains were categorized as Multidrug-Resistant (MDR) strains due to resistance to more than one antibiotics [5,6].

There are more than one ways to manage typhoid fever caused by an MDR strain but none of them is perfect. Fluroquinolones like ciprofloxacin are potent antibiotics and most strains of Salmonella typhi are susceptible to them [7]. But when it comes to pediatric age group, these antibiotics are shown to have cartilage and bone toxicity in growing children [8]. Their adverse effects on metaphysis of bones limit their use in children [9]. Then comes the role of cephalosporin (CSP) antibiotics. Third generation cephalosporin (CSP) drugs, like cefotaxime and ceftriaxone, have been shown to eradicate more than 90% of strains successfully [10,11]. At the same times, these drugs are available only in parenteral preparations that need mandatory indoor admissions besides a high cost of these drugs and the risk for the development of resistance [12].

Here comes the role of Cefixime which is a third generation CSP antibiotic available in oral preparation at an affordable cost. Cefixime has a spectrum coverage comparable to other third generation CSP antibiotics [13,14]. An experimental trial conducted in Egypt found Cefixime to be effective in treating typhoid successfully [15]. Cefixime has also been used in the treatment of MDR typhoid in Pakistan previously [16]. This study has evaluated the efficacy of Cefixime in the treatment of culture-confirmed Salmonella typhi infection as compared to chloramphenicol.

2. METHODOLOGY

A randomized controlled trial was carried out, during May 2017 to October 2017, in the Department of Pediatric Medicine at District Headquarter (DHQ) Teaching Hospital, Sahiwal which is a district level tertiary care healthcare facility in Pakistan. Approval from the ethical committee of the hospital was followed by inclusion of patients who presented during June to September 2017 based on following criteria:

2.1 Inclusion Criterion

- Patients with age between 2 and 12 years.
- Patients with the history of fever for 2-4 days.
- Patients diagnosed with typhoid fever and confirmed by isolation of *S. typhi* Strain from the blood.

2.2 Exclusion Criteria

- Patients who were having any co-morbidity.

- Patients with concurrent infections.
- Patients who were unconscious or had Glasgow Coma Scale (GCS) score of 13 or less.
- Patient with suspicion of typhoid fever but negative culture.
- Patients whose parents/guardians were not willing for indoor admission.
- Patients whose parents/guardians didn't consent to inclusion in the study.

A sum of 60 patients were selected for the sake of this study after calculation of sample size in the population of Sahiwal District (Sahiwal District has 381,645 people between the age 2-12 years) using WHO sample size calculator for Biomedical research and studies by taking level of confidence to be 95% and acceptable margin of error within 5%. These patients were divided into Group A and Group B with 30 patients in each group, by the process of probability systematic sampling technique, applied on the list formulated in the sequence patients reported to Pediatric Outdoor. Preceding the signing of detailed informed consent, patients were made aware of treatment options and treatment was started at once.

Patients in group A received Cefixime at a dose of 10 mg/kg/day in 2 divided doses while patients in group B received Chloramphenicol at a dose of 50 mg/kg/day in 4 divided doses. Plan of treatment was to continue the antibiotic therapy for a total of 10 days.

Patients were admitted to Pediatric indoor and daily evaluation was done for their clinical condition. Defervescence of fever was recorded for each patient in terms of the number of days starting from hospital admission. In patients who responded to treatment before completion of 5 days of treatment, treatment was only continued for 5 more days unless child became febrile anytime again in which case a course of antibiotic was continued for a total of 10 days as per initial treatment plan. In patients who had a persistent fever even after 7 days of prescribed treatment, an alternative antibiotic was started, the discussion of which is out of the scope of this study. For the sake of this study, those patients were categorized as non-responders or unsuccessful cases. All patients were also followed up for another 3 weeks after discharge from the indoor ward.

Version 20 of the software Statistical Package for Social Sciences (SPSS) was used to analyze the collected data. Comparison of the two treatment options was made using independent sample t-test. The P value below 0.05 was considered significant statistically.

3. RESULTS

Patient included in this study ranged from 2-12 years of age with an average age of 7.1 years. 25 patients were in 2-5 years age group, 24 patients were in 6-9 years ago group and 11 patients had age above 9 years. Among the patients included in the study, there were 40 males (67%) and 20 females (33%) patients. The mean temperature of the patients as measured at the time of admission using mercury thermometer was 102'F (in axilla). The mean or average time of presentation to the pediatric OPD was 3rd day of fever. On the first day of admission, 69% of patients had liver palpable below costal margin while in 13% of patients both liver and spleen were palpable.

Table 1 compares the days of treatment after which fever settled in patients included in this study. In Group A most of the patients had responded to Cefixime within the first week with exception of only 2 out of 30 patients who were later on switched to intravenous CSP antibiotics and were categorized as non-responders or unsuccessful cases for the sake of this study. While in Group B, no patient responded within first 72 hours and more than half of patients had to be switched to alternative treatment after 7 days.

Table 1. Defervescence of fever in both groups (n=60)

Time of Defervescence (in days)	Treatment Groups	
	Group A (n=30)	Group B (n=30)
3	6	0
4	5	2
5	3	2
6	10	6
7	4	3
Non-responders	2	17
Total	30	30

Independent sample t-test P Value = 0.01

Table 2 compares the rate of cure in both groups included in the study. Of 17 patients, unsuccessfully treated with Chloramphenicol, 15 were started on Oral Cefixime and all of them were successfully cured within 5 days of this alternate treatment. Two patients (11-year and

Table 2. Cure rate for both groups included in the study

Groups	No of patients	Cured	Not cured	Efficacy
Cefixime*	30	28	2	93.3%
Chloramphenicol	30	13	17	43.3%

Overall cure rate of Cefixime was 43/45, i.e. 95.5% (P value = 0.005)

12-year-old) were started on ciprofloxacin due to severe illness and were successfully cured. Considering Cefixime, it cured a total of 43 patients out of 45 with a cure rate of more than 95% as compared to cure rate of chloramphenicol, i.e. below 45%.

No significant adverse effects were reported or recorded in any of the 60 patients.

Cost of the 10-day treatment with Cefixime and Chloramphenicol differed widely due to wide variation in body weight of pediatric patients.

4. DISCUSSION

Purpose of this study was to compare the efficacy of Cefixime in the treatment of typhoid fever against the cure rate of chloramphenicol, which had been a treatment of choice for many years before resistant strains of Salmonella typhi appeared. Results of our study were comparable to older larger scale studies in Pakistan and other countries with a cure rate of Cefixime at 95.5% and that of chloramphenicol at 45% [12,13].

5. CONCLUSION

This study carried out on a small scale confirmed that Cefixime used in Pediatric patients of typhoid fever at a dose of 10 mg/kg/day is not only safe but an effective choice of antibiotic with high cure rate. Oral preparation also makes this option much more attractive.

CONSENT

All authors declare that 'written informed consent was obtained from the parents/guardians of the patients for inclusion in the study, treatment with any of the two pharmacological drugs as per randomized sampling, publication of this study and its analyzed results along with drawn conclusions.

ETHICAL APPROVAL

Ethical approval was granted by Ethical Board of Research Committee, SMC, Sahiwal vide ethical clearance no. SMC/679/2017 on May 22, 2017.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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