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Antimicrobial Activity of Azithromycin versus Ciprofloxacin in the Treatment of Uncomplicated Enteric Fever in Children and Adolescents: Preclinical Trial

Zona Irfan[1*], Ali Nawaz Bijarani[2], Yousra Muhammad Pervaiz[3], Fauzia Perveen[4], Shahid Pervez Shaikh[5] and Humaira Arif[6]

[1]Department of Nursing, National University of Medical Sciences, Islamabad, Pakistan
[2]Armed Forces, Bone Marrow Transplant Center, Rawalpindi, Pakistan
[3]Department of Nursing, Armed Forces Bone Marrow Transplant Center, Rawalpindi, Pakistan
[4]Department of Nursing, Armed Forces Post Graduate Medical Institute, Rawalpindi, Pakistan

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***Corresponding Author:**
Zona Irfan
Department of Pathology, Fazaia Ruth Pfau Medical College, Karachi, Pakistan
zonairfan@gmail.com

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ABSTRACT

Typhoid fever, or enteric fever, is an infectious disorder particularly prevalent in Pakistan. Salmonella Typhi is the common and occasionally fatal cause of enteric fever. **Objective:** To compare the antimicrobial activity of Azithromycin versus Ciprofloxacin in the treatment of uncomplicated enteric fever in children. **Methods:** This was a comparative cross-sectional study conducted at the Department of Microbiology at Ziauddin University Hospital, Karachi. It lasted six months, from 3 January 2020 to 2 July 2020. There were 152 blood samples in all. According to Clinical and Laboratory Standards Institute guidelines, the antibiotic susceptibility of the isolates was assessed using the Modified Kirby Bauer disc diffusion method on Muller-Hinton agar. **Results:** When treating typhoid fever in children with simple enteric fever, the susceptibility pattern of Salmonella Typhi revealed that azithromycin was more efficient than ciprofloxacin in preventing the growth of Salmonella Typhi across all samples. Ciprofloxacin showed resistant bacteria. **Conclusion:** Azithromycin seems to be more clinically effective than ciprofloxacin in treating children's simple enteric fever when treating typhoid fever.

INTRODUCTION

Children are more prone than adults to the spread of infectious diseases because their immune systems are still developing [1]. Typhoid fever, or enteric fever, is one of these infectious disorders that is particularly prevalent in Pakistan. Salmonella Typhi is a common and occasionally fatal cause of enteric fever. Its feco-oral method of transmission and inadequate sanitation make it most common in impoverished nations [2]. Reported estimates of the annual incidence of enteric fever are global, ranging from 12 million to 27 million cases. The estimated death toll varied from 129,000 to 223,000 based on data from the year 2017, as per the epidemiological analyses [1, 2]. Interventions focusing on early diagnosis and appropriate clinical treatment, along with risk factor prevention, can improve the outcomes of enteric fever. Chloramphenicol used to be the recommended medication. however, it is no longer in use due to adverse effects, relapses, and widespread bacterial resistance. Next, co-trimoxazole and ampicillin were employed as suitable and efficient substitutes. However, in the 1980s, S. typhi developed resistance to ampicillin, co-trimoxazole, and chloramphenicol. As a result, fluoroquinolone use increased. Fluoroquinolone resistance also gradually emerged [3]. Multi-drug resistant bacteria, resistant to

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fluoroquinolones, ampicillin, co-trimoxazole, and chloramphenicol, increased in frequency from 19% in 1987 to 100% in 1993, declining to 5% by 2000 [4]. At present, azithromycin and extended-spectrum cephalosporins (ceftriaxone, cefixime) are being recommended as therapeutics for enteric fever [5]. When a single therapy fails to provide the desired results, a combination of these medications is required to potentially expand the antibacterial spectrum through pharmacological synergism. Azithromycin is more effective than many other competing medications in reducing recurrence, length of hospital stay, and clinical failure rate, according to many trials. It is also well tolerated [6]. Because of this, physicians are now using azithromycin and cephalosporins as the final treatments for which there is solid evidence from clinical trials. There is evidence of the introduction of a cephalosporin-resistant strain of Salmonella Typhi today, in addition to the bacterial burden of enteric fever that is currently prevalent in South Asia [7]. Fluoroquinolones, such as Ciprofloxacin, are being used as the first-line treatment due to the advent of multidrug-resistant strains (MDR) to first-line antibiotics including Chloramphenicol, Ampicillin, and Trimethoprim-sulfamethoxazole [8]. Although azithromycin and ciprofloxacin are among the oral antibiotics that are most frequently administered in our area as an empirical treatment for uncomplicated enteric fever, concerns about treatment response differences still exist. Recently, a significant typhoid outbreak in Pakistan has been linked to Salmonella typhi genetic variants that are highly resistant to drugs. Multiple cases of these strains have been documented [9]. Along with resistance, azithromycin and ciprofloxacin have been associated with varying fever clearance time (FCT), which averages 4-5 days. This has been connected to less-than-ideal therapeutic response, elevated morbidity, treatment expenses, and healthcare burden [10]. The best oral antimicrobial treatment for simple typhoid fever is unknown because of the constantly shifting pattern of microbial resistance and the inconsistent responses to medications.

This study aims to investigate the comparative efficacy of azithromycin and ciprofloxacin in our local community of children with uncomplicated enteric fever, as to our knowledge there is currently no data available on it.

METHODS

The comparative cross-sectional study was done by the microbiology Department of Ziauddin University Hospital in Karachi. The study was for six months from 3rd January 2020 to 2nd July 2020. After obtaining informed consent, all blood samples from inpatients and outpatients were taken for sensitivity and culture. Male and female participants in the study ranged in age from 1 to 20 years (Children and adolescents). Duplicate and repeat samples from the same patient, as well as blood samples for sensitivity and culture that showed growth other than bacteria, including yeast or fungus, were not included. The management of Ziauddin Hospital granted authorization, and the institutional ethics committee provided written approval IRB: 0611118ZIMIC. Using the WHO Sample size calculator and the Meropenem sensitivity statistics of 87% margin of error, 9%, and 95% confidence interval, the sample size was determined to be 54 per group. All blood cultures were obtained from a peripheral vein while adhering to the proper aseptic protocols before starting any antibiotic therapy, for the pediatric population, pediatric BACTEC bottles were used. The sample was cultured for five days at 35.5 °C ± 1.5°C in a BACTEC 9240 blood culture apparatus with a blood-to-broth ratio of 1:10. The BACTEC device uses fluorescence sensing technology to identify the growth of microorganisms. To evaluate the amount of microbiological development that the device's flag and audible sound could identify, a gram-stained smear of the broth was used. To isolate the bacteria, they were then sub-cultured on 5% sheep blood agar, chocolate, and Mac-Conkey agar plates and incubated at 37°C for 18 to 24 hours. Plates of sheep blood agar, chocolate and Mac-Conkey agar were pre-incubated to rule out any possibility of mishandling during plate preparation. Mac-Conkey agar plates were maintained in an aerobic incubator at 37°C, while sheep blood agar and chocolate agar were incubated in a capnophilic atmosphere with 5–10% CO2. Standard microbiological methods were used to identify the S. typhi clinical isolates, including gram staining, the oxidase and catalase tests, motility, triple-sugar iron (TSI) fermentation, colony morphology, and, for the final confirmation, biochemical tests of the analytical profile index (API 20 E) [10]. Following Clinical and Laboratory Standards Institute (CLSI) recommendations, the isolate's antibiotic susceptibility patterns were assessed in two treatment groups one getting azithromycin (Group A) and the other receiving ciprofloxacin (Group B) using the Modified Kirby Bauer disc diffusion method on Muller-Hinton agar. For 18–24 hours, the Muller-Hinton agar plates were kept in an aerobic environment at 35°C ± 2°C. Version 20 of the Statistical Package for the Social Sciences was used to enter and analyze the data. Data were shown as a percentage and as frequency. The Chi-square test was used. p-value less than 0.05 was regarded as significant.

RESULTS

The demographic analysis of 105 oncology and bone marrow transplant nurses reveals a predominantly experienced and well-educated workforce, with 47.6% aged 31–40 years and 89.5% being female. Most

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participants (57.1%) held a bachelor's degree, while 35.6% had over 15 years of nursing experience. However, training in chemotherapy preparation varied, with 30.5% receiving training only once and an equal percentage having no training, indicating potential gaps in professional development. Despite a strong awareness of antimicrobial policies (83.8%) and chemotherapeutic spill kits (96.2%), the presence of a minority lacking knowledge underscores the need for continuous education. Overall, while the nurses demonstrate significant knowledge and experience, standardized training and reinforcement of key policies are essential to enhance patient care and safety in oncology settings (Table 1).

Table 1: Antimicrobial Susceptibility Pattern According to Age

Age Group	Antimicrobial Susceptibility	Group A (Azith -15µg)	Group B (Cipro -5µg)	p-value
1-10 Years	Sensitive	38 (100%)	8 (21%)	0.01
	Resistant	0 (0%)	30 (79%)	
10-20 Years	Sensitive	38 (100%)	3 (8%)	0.02
	Resistant	0 (0%)	35 (92%)	
Total		76	76	152

Chi-Square Test was applied. p-value ≤0.05 is considered as Significant. Group A (Azith-Azithromycin 15µg): Refers to the antimicrobial susceptibility test using Azithromycin with a 15µg disc. Group B (Cipr-Ciprofloxacin 5µg): Refers to the antimicrobial susceptibility test using Ciprofloxacin with a 5µg disc.

Analysis based on gender revealed that 45 (90%) of male were sensitive to Azithromycin, while 5 (10%) were resistant. In comparison, 10 (17%) of male were sensitive to Ciprofloxacin, while 50 (83%) were resistant. Azithromycin was significantly more effective in male compared to Ciprofloxacin (p-value=0.001). For females, 7 (38%) were sensitive to Azithromycin, while 12 (62%) were resistant. Similarly, 9 (38%) of females were sensitive to Ciprofloxacin, while 14 (63%) were resistant. No significant difference in drug response was observed between Azithromycin and Ciprofloxacin in females (p-value=0.5). Azithromycin demonstrated greater efficacy compared to Ciprofloxacin in treating uncomplicated typhoid fever, particularly in younger age groups and male. The p-value for the 1–10-year age group was 0.01, for the 10–20-year age group was 0.02, for male was 0.001, and for female was 0.5 in table 2.

Table 2: Antimicrobial Susceptibility Pattern According to Gender

Gender	Susceptibility	Group A (Azith -15µg)	Group B (Cipro -5µg)	p-value
Male	Sensitive	45 (90%)	10 (17%)	0.001
	Resistant	5 (10%)	50 (83%)	
Female	Sensitive	7 (38%)	9 (38%)	0.5
	Resistant	12 (62%)	14 (63%)	
Total		69	83	152

The Chi-Square Test was applied. p-value ≤0.05 is considered as Significant. Group A (Azith-Azithromycin 15µg): Refers to the antimicrobial susceptibility test using Azithromycin with a 15µg disc. Group B (Cipr-Ciprofloxacin 5µg): Refers to the antimicrobial susceptibility test using Ciprofloxacin with a 5µg disc.

DISCUSSION

Young children in Pakistan are at risk of contact with typhoid infection due to improper hygiene. The increasing resistance to second-line anti-typhoid agents is a public health concern. The incidence of superbugs in children is a public health emergency. The current state of antimicrobial surveillance in Pakistan needs urgent attention to prevent antibiotic resistance and appropriate stewardship. In impoverished nations like Pakistan, enteric fever is a serious health issue that requires a treatment option that is both affordable and effective to be employed often with limited resources at our disposal [11]. Two typical antibiotics used to treat typhoid fever are azithromycin and ciprofloxacin. However, due to variations in pharmacodynamics, resistance patterns, and patient tolerability, these drugs' efficacy can vary, especially when administered in children. Azithromycin is a macrolide antibiotic that inhibits protein synthesis in bacteria, halting growth and exerting a bacteriostatic effect, particularly effective against Gram-positive and Gram-negative pathogens like Salmonella Typhi [12]. Ciprofloxacin, a fluoroquinolone antibiotic, inhibits DNA gyrase and topoisomerase IV, resulting in bactericidal activity, making it popular for treating typhoid fever due to its potent Gram-negative bacteria resistance [13]. This study, which compared azithromycin and ciprofloxacin for treating children's uncomplicated enteric fever, showed that azithromycin was highly responsive, with clinical efficacy of over 90% (p-value is significant), which is consistent with the findings of many other studies [14-16]. Azithromycin treatment was found to be effective in a small number of adult studies, but not significantly enough in children, despite our findings that the majority of children responded favourable to azithromycin [17]. In this investigation, azithromycin was able to limit growth by over 90%. Azithromycin's exceptional intracellular penetration, which produces potent therapeutic efficacy primarily against intracellular S. typhi, may account for its high responsiveness. The likelihood of Salmonella Typhi strains developing resistance to antibiotics is one of the most important factors affecting the selection of antibiotic treatment for typhoid fever. There is a growing demand for alternative antibiotics due to treatment failures caused by fluoroquinolone resistance, notably in South Asia, which includes ciprofloxacin. Mutations in the bacterial DNA

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gyrase and topoisomerase genes' quinolone resistance-determining regions (QRDR) are frequently the cause of this resistance [18]. Azithromycin has been shown in numerous studies to be clinically effective in treating pediatric typhoid fever. Numerous studies have also demonstrated that azithromycin is more effective than ciprofloxacin in treating typhoid fever in children [19]. When compared to ciprofloxacin, clinical investigations have shown that azithromycin had higher cure rates and a quicker time to defervescence, or the reduction of fever [20]. In addition, compared to ciprofloxacin, azithromycin is generally well-tolerated in children and causes fewer gastrointestinal adverse effects. Despite its effectiveness, ciprofloxacin can cause side effects in juvenile children, including tendinitis, gastrointestinal distress, and infrequently, arthropathy. In the case of young patients, azithromycin is a safer choice due to these possible side effects [21].

CONCLUSIONS

It was concluded that azithromycin seems to be more clinically effective than ciprofloxacin in treating children's simple enteric fever when treating typhoid fever. Because of its daily dosage, tolerability, and lower risks of resistance, azithromycin is a safer substitute. For management to be effective, resistance tendencies must be regularly monitored.

Authors Contribution

Conceptualization: ZI, YMP, FP
Methodology: ZI, YMP, FP
Formal analysis: SPS, HA
Writing review and editing: ZI, ANB, YMP, FP, SPS, HA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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