

ORIGINAL ARTICLE

Comparison of Efficacy of Ciprofloxacin and Co-Trimoxazole in Escherichia Coli Urinary Tract Infection

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ABSTRACT

Objective: To compare the efficacy of ciprofloxacin and co-trimoxazole in urinary tract infection due to Escherichia Coli.

Study Design: A cross-sectional study.

Place and Duration of Study: This study was conducted at the Department of Medicine, Muhammad Teaching Hospital (MTH), Peshawar, Pakistan from 1st July 2022 to 31st December 2022.

Methods: Patients were randomly and consecutively assigned to either group by using lottery method (double blind). A total of 194 patients diagnosed with urinary tract infection due to E coli were randomly divided into two groups, 97 patients in each group, using 54% efficacy of ciprofloxacin, 74% efficacy of Co-Trimoxazole, 95% confidence level, and 90% power of test, using WHO software. "Group-A" for Ciprofloxacin 500mg BD and "Group-B" for Co-Trimoxazole 960mg BD. All the recruited patients were followed up after the 48th hour of their treatment and results were recorded. The chi-Square test was applied to compare the efficacy results of both drugs where a P Value < 0.05 was considered as significant value.

Results: The mean age of group A participants were 48.4 + 11.1 years, whereas, in group B it was 48.2 + 11.5 years. There were 69.1% males and 30.9% females in group A compared to 80.4% males and 19.6% females in group B. After the 48th hour of end treatment, efficacy was 79.3% and 50.5%, in groups A and B respectively (*p-value* = 0.000).

Conclusion: As compared to Cotrimoxazole, Ciprofloxacin is more effective in treating E. coli-caused urinary tract infections.

Keywords: Bacteriuria, Ciprofloxacin, Co-Trimoxazole, Cystitis, Escherichia, Pyelonephritis, Pyuria.

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Introduction

Infection of the urinary tract by pathogenic bacteria is termed Urinary Tract Infection (UTI); which includes symptomatic patients having cystitis, prostatitis, and pyelonephritis. UTIs may be uncomplicated or complicated. Uncomplicated UTI represents those UTI cases that are acute and without any co-morbid conditions such as acute pyelonephritis or cystitis, females without pregnancy or anatomic abnormalities, outpatient department male, or without instrumentation of the urinary tract; complicated UTI is a catch-all term that includes all other types of UTI.¹ nowadays, it

encompasses one of the most prevalent diseases globally, averaging about 150 million newly diagnosed cases annually and people of all ages are prone to UTI.² The UTIs occur more in elderly patients with a prevalence of 51.04% than in pediatric patients and affect women more commonly (66.66%).³ UTIs are mostly not life-threatening and do not result in any irreversible damage. However, when pyelonephritis occurs, there is a greater risk of irreparable tissue damage with a higher risk of leading to bacteremia. Due to the acute course of UTI disease and the risk of developing pyelonephritis and leading to permanent renal tissue damage, most patients are prescribed with longer duration of antibiotics to prevent recurrence.⁴ Escherichia Coli (E. Coli) is one of the chief causes of UTI in over 80% of cases.^{4,5} Fluoroquinolones (Ciprofloxacin) have been considered an ideal drug for the treatment of UTIs since their diverse mechanisms of action seem to prevent resistance by E. coli. Ciprofloxacin is also potent against a large number of E. coli strains compared to other commonly used drugs. Moreover, ciprofloxacin is comparatively less expensive too.⁶ The resistance of all UTI isolates, especially E. Coli, to ciprofloxacin was found to be 62% by Ullah H. et al. (Hence 38% Efficacy), and this resistance was observed to increase continuously.² Hooton TM demonstrated on the criteria by Infectious Diseases Society of America (IDSA), ciprofloxacin (250 mg BID for 3 days) for acute uncomplicated cystitis is about 90% effective and is 96% effective in 500 mg BID for 7 days dosage, in Acute Uncomplicated Pyelonephritis.⁷ On the other hand, Akram M. et al. observed in their study that Co-Trimoxazole was effective in only 25% of cases and was resisted by E. Coli in 75% of cases. They further added that resistance of UTI isolates against Co-Trimoxazole varies in the USA, Europe, Senegal, Spain, Taiwan, and Israel as 18.6%, 14.1%, 55%, 33%, 56%, and 26% (Hence Efficacies 81.4%, 85.9%, 45%, 67%, 44%, and

74%) respectively.³ The emergence of resistance to the described antibiotics in the management of UTIs and the decline in their efficacy is indeed a major public health concern. This is specifically more important in developing countries like Pakistan, where besides high rate of poverty, illiteracy and poor hygienic protocols, fake and spurious drugs of lower standards are often used. If immediate actions are not taken to control this situation, we may be faced with the problem of searching for new drugs to treat bacterial infections causing UTIs. The current study is designed in this regard to find statistics about the efficacies of Ciprofloxacin and Co-Trimoxazole for the UTIs in our local population at present. Urinary Tract Infections have a significant burden on the patients and the use of inappropriate and ineffective drugs can cause more side-effects and more damage. This can lead to more psychological and physical burden on the patients which itself needs further treatment and thus more expenditure. By finding the local statistics about efficacy and safety of the two antibiotics, we will be able to formulate a proper protocol describing the best antimicrobial agent for the empirical treatment of the patients presenting with UTIs. Moreover, this study will help us gain more information about the different types of pathogens that cause UTIs and their pattern of susceptibility which may aid in appropriate empirical treatment. These results of the current study will be shared with different healthcare institutions in order to improve the in-practice treatment guidelines so as to lower the morbidity and mortality rate and better care for UTI patients.

Methods

This study was conducted at the Department of Medicine, Muhammad Teaching Hospital (MTH), Peshawar, Pakistan from 1st July 2022 to 31st December 2022 after obtaining approval from the Ethical Review Committee of the hospital held on 20th June 2022 vide letter no: MTH/EC/76/2022. By using a randomized controlled study design, 194 patients were selected who presented with UTI caused by E.

coli and were randomly divided into two groups, 97 patients in each group, using 54% efficacy of ciprofloxacin⁷, 74% efficacy of Co-Trimoxazole³, 95% confidence level and 90% power of test using WHO software. All patients were followed up after the 48th hour of treatment and results were noted.

Sampling Technique: Non-probability consecutive sampling.

Inclusion Criteria

1. Patients with uncomplicated UTI due to E. Coli on urine culture and have given consent.
2. Patients of either gender with age ≥ 18 years.

Exclusion Criteria

1. Patients who have taken antibiotics in the last five days at the time of presentation.
2. Immunocompromised patients.
3. Patients with impaired renal functions.
4. Patients with urinary tract anatomical abnormalities and urinary tract calculi.

Data Collection Procedure

This study was preceded by the ethical approval from the ethical and research committee of the institution Muhammad Teaching Hospital Peshawar. All patients from the out-patient department fulfilling the inclusion criteria were recruited for the study. The patient was recruited after written informed consent was obtained. The recruited patients have undergone routine investigations like Full Blood Count, Ultrasound of the Urinary system, Renal Function tests, and Random Blood Sugar to satisfy the exclusion criteria. The patients were then being divided into two groups randomly: "Group-A' for

Ciprofloxacin 500mg BD and 'Group-B' for Co-Trimoxazole 960mg BD, both groups receiving treatment for 10 days. A detailed history with a thorough examination was obtained from all the recruited patients. The diagnosis of UTIs was based on the mentioned criteria. Urine culture was performed by collecting urine samples in a sterile bottle and then subjecting it to growth for bacteria using Kled or MacConkey agar incubated at 37C° in an incubator for 24 hours in the hospital laboratory.

Data Analysis Procedure

SPSS's latest version of was used to analyze all the collected data from patients. Continuous variables such as age were expressed as Mean ± SD. Categorical variables such as gender and efficacy, were expressed in Frequencies and percentages. The chi-Square test was applied to compare the efficacy results of both drugs where P Value < 0.05 was considered a significant value.

Results

The overall average age of the participants was 48.3 ± 11.3 years, whereas the average age of patients included in group A was 48.4 ± 11.1 years while in group B it was 48.2 ± 11.5 years. Gender-wise comparison of the groups showed that in group A; there were 67(69.1%) males and 30 (30.9%) females whereas; in group B there were 78(80.4%) males and 19(19.6%) females. The results were statistically insignificant (*p-value* = 0.069). (Table-1).

Patients of both groups (groups A and B) were also further distributed in 4 age categories i.e. ≤40 years, 40.01-50 years, 50.01-60 years and >60 years. This

Table-1: Gender-based distribution of patients in both groups (n=97 in each)

		Group		Total
		Group A (CIPRO)	Group B (CO TRI)	
Gender	Male	67	78	145
	Female	30	19	49
Total		97	97	194

distribution reflected that age has no relationship with UTI due to E. coli however, slightly more patients were observed in age group above 50 years as evident from the tables. (Table-2).

ON follow-up, a urine culture was performed to detect the presence or absence of infection. It was observed that in group A, 77(79.3%) patients had negative culture and in group B 49(50.5%) patients

had culture-negative reports of urine at the 48th hour of treatment and overall, in the whole study population (194), negative culture was found in 126(63.9%) of the patients. (Table- 3).

Culture negativity at the 48th hour of treatment was considered efficacy for the treatment. According to this, efficacy in group A was recorded in 77(79.3%) of patients while in group B it was recorded in

Table -2: Age group distribution of patients in both groups (n=97 in each)

		Group		Total
		Group A (CIPRO)	Group B (CO TRI)	
Age Groups	≤ 40.00 yrs	29	29	58
	40.01 -50.00 yrs	19	29	48
	50.01 -60.00 yrs	29	20	49
	≥60.1 yrs	20	19	39
Total		97	97	194

49(50.5%) of patients. The difference in the results was statistically significant with a p -value <0.001 by applying chi-square test. (Table-4).While stratifying

the efficacy of the drug in group-A gender-wise, we observed that males tend to show more efficacies as compared to females with p -value = 0.038. (Table-5).

Table-3: Comparison of efficacy between both groups/ culture report after 48 hours of end of treatment in both groups (n = 97 each)

			Group		Total	Chi-square (P -value)
			Group A (CIPRO)	Group B (CO TRI)		
Urine Culture result after 48 hours/ Efficacy of the Drug	Yes	77	49	126	17.752(≤0.00 1)	
	No	20	48	68		
Total		97	97	194		

Table- 4: Gender stratification of efficacy in group A (n = 97)

		Efficacy of the Drug		Total	Chi-square (P -value)
		Yes	No		
Gender	Male	57	10	67	4.290(0.038)
	Female	20	10	30	
Total		77	20	97	

Table- 5: Gender stratification of efficacy in group B (n = 97)

		Efficacy of the Drug		Total	Chi square (P -value)
		Yes	No		
Gender	Male	39	39	78	0.042(0.837)
	Female	10	9	19	
Total		49	48	97	

In group B, however, the scenario was different with no change in terms of efficacy of the treatment in

male and females with p-value = 0.837. (Table-6). While stratifying the efficacy of the drug in group A

Table - 6: Age groups wise stratification of efficacy in group A (n=97)

		Efficacy of the Drug		Total	Chi-square (P-value)
		Yes	No		
Age Groups	≤40.00 yrs	29	0	29	26.42(≤0.000)
	40.01-50.00 yrs	19	0	19	
	50.01-60.00 yrs	19	10	29	
	≥60.1 yrs	10	10	20	
Total		77	20	97	

with respect to age groups, we observed that younger age tends to show more efficacy as

compared to older age p value <0.001. (Table-7).

Table - 7: Age groups wise stratification of efficacy in group B (n=97)

		Efficacy of the Drug		Total	Chi-square (P-value)
		Yes	No		
Age Groups	≤40.00 yrs	10	19	29	50.788(≤0.001)
	40.01 to 50.00 yrs	29	0	29	
	50.01 to 60.00 yrs	10	10	20	
	≥60.1 yrs	0	19	19	
Total		49	48	97	

Discussion

Although majority of the adults with UTIs have uncomplicated infections and are treated with antibiotics empirically, it is still a major issue for the health system, more specifically in women, where each year 10% of women get bladder or other urinary tract infection.⁸ Rarely, UTI results in grave and long-lasting renal damage in those patients harboring any associated abnormalities such as renal tract anomalies, diabetes mellitus, or pregnancy.⁹ UTI is rare in young males who haven't had any instrumentation of the genitourinary tract, but common in homosexuals. However, it is not uncommon in males aged of 50 or more especially due to prostatic gland complications. About 20-50% of females and 5-20% in institutionalized care had reported asymptomatic bacteriuria.¹⁰ In childhood, UTI may lead to permanent kidney deterioration leading to end-stage failure of kidneys at a young age.¹¹

About 10% of urinary tract infections are caused by saprophytic staphylococci in sexually active women. Community-acquired pathogens are usually

responsive to commonly used antimicrobial drugs. On the other hand, E coli results in only half of the nosocomial infections while the rest are caused by P. aeruginosa, klebsiella, staphylococci, serratia, proteus, enterococci, yeasts, etc.¹² About 60-86% of E. coli in cystitis are resistant to ampicillin and cephalosporins in vitro,^{13,14} and trimethoprim resistance is also on the rise in different regions of the world.¹⁵ Therefore, alternative therapeutic drugs are the need of the day in order to cure such cases. The fluoroquinolone group is one of the antimicrobial agents that are currently evaluated for UTI treatment. The more recently developed drugs in this group i-e, norfloxacin, ciprofloxacin, and ofloxacin are effective for all kinds of UTIs when used for a period of 7-10 days.^{16,17} We also confirmed that ciprofloxacin is as potent compared to the prescribed regimen of trimethoprim-sulfamethoxazole used for UTI caused by E. Coli. The cure rates at the 48th hour after treatment in terms of the culture of urine observed here with ciprofloxacin are higher than the conventional regime of trimethoprim-

sulfamethoxazole in this study.

According to IDSA 1999 guidelines trimethoprim-sulfamethoxazole, one tablet per oral route in double dose, BID for 3 days, is recommended for any uncomplicated case of UTIs and effectively covers almost 95% of such cases.¹⁸ While a One-day course, due to its lower coverage (almost 85%) is not advised as primary treatment. Similarly, 5 days, one week or two weeks of course also have no advantage over 3-day courses as they do not increase the probability of cure and is more likely to cause adverse reactions of the drugs. However, in cases of pyelonephritis and complicated infections, treatment is advised for one to two weeks. In case of hypersensitivity to sulfa drugs, trimethoprim, in 100 mg dose, twice daily can be used, with comparable results to trimethoprim-sulfamethoxazole in uncomplicated infections. Compared to amoxicillin and cephalexin (β -lactam antibiotics), Trimethoprim-sulfamethoxazole are advantageous. Firstly, trimethoprim-sulfamethoxazole has a higher cure rate, even when resistance to the drug is non-contributory. Second, it prevents recurrent UTI over the next few months, which is mainly because this drug also kills enterobacteriaceae.¹⁹

The IDSA recommendation states that when in a community there is 10-20% resistance to trimethoprim sulfamethoxazole then other drugs, such as fluoroquinolones should be used for empirical treatment, having the highest efficacy. Analysis by Le and Miller demonstrated that fluoroquinolones are cost-effective to trimethoprim-sulfamethoxazole in more than 22 % resistance: primarily due to failed treatment, hospital revisits, and laboratory expenses.²⁰ Other studies showed similar results with cost-effectiveness of fluoroquinolones compared to trimethoprim-sulfamethoxazole at 19-21% resistance.²¹

Fluoroquinolones are highly effective against uropathogens in UTI as they also kill enterococci like trimethoprim-sulfamethoxazole. Although fluoroquinolones cost more than trimethoprim-sulfamethoxazole, but it is acceptable, due to its high success rate in resistant cases. Recently different drugs in fluoroquinolones group have been manufactured and approved for all the cases of UTI in the US. These include ofloxacin, levofloxacin,

ciprofloxacin, norfloxacin, gatifloxacin and moxifloxacin. Moxifloxacin is also included in fluoroquinolone, but it is not ideally approved for UTI treatment because of its minimal urinary concentrations and hepatic metabolism.²² Gemifloxacin, is used for respiratory tract infections but not for UTIs yet.²³

In another research work in a hospital admitted elderly patients with indwelling catheter's associated UTIs were subjected to oral ciprofloxacin 100mg BID and 250mg BID, where *P. aeruginosa* caused 24% of infections. At 28 days follow-up, the successfully cured cases were 94 percent and 88 percent, respectively. There were minimal side effects. Even in complicated UTIs ciprofloxacin is a safe drug when administered orally.²⁴ However, in a study by Goettsch WG et al. treatment with trimethoprim and nitrofurantoin showed a 14.4% treatment failure rate in patients, and with fluoroquinolones, it was 9.6%.²⁵

In another study, treatments with both ciprofloxacin and co-trimoxazole groups showed a 91% success rate of therapy.²⁶ Ciprofloxacin therapy failed in 7 cases in which, three were due to recurrence and two had side effects that needed to stop medication, while two required hospitalizations due to persistent symptoms. Similarly, trimethoprim-sulfamethoxazole therapy was also associated with six failure cases in which four were due to relapse, one had persistent symptoms of infection, and one had to change medication due to drug side effects. With trimethoprim-sulfamethoxazole, 32% of the patients experienced mild adverse reactions as compared to 17% with ciprofloxacin ($P = 0.026$). Thus, it was shown that ciprofloxacin had fewer side effects as compared to trimethoprim-sulfamethoxazole in UTI patients.

For uncomplicated cases of UTIs, an antibiotics course for three days is recommended by IDSA.¹⁸ Single-dose treatment with fluoroquinolones is not only less effective but also has more side-effects compared to a 3-days course.¹⁹ But in some cases, it appears to be as effective as a 3-day course.²⁷ But with this approach symptoms may remain for several days after therapy. Research on single-dose regimen is still deficient and unfortunately, drug resistance in uropathogens that causes uncomplicated UTI is

increasing.²⁸ Data analysis of the uncomplicated UTI patients presenting to the Emergency Department reported an increase in resistance to trimethoprim-sulfamethoxazole in uropathogens. Results showed rise in the resistance from 8% (1992) to 25.1% (2022).²⁹ Ampicillin, cephalothin, and trimethoprim also showed temporal drug resistance increment. Another study on uropathogenic causing uncomplicated UTIs reported that resistance to trimethoprim-sulfamethoxazole and other antibiotics should be minimized by giving treatment according to bacterial sensitivity.³⁰ We have demonstrated that ciprofloxacin is effective in uncomplicated UTIs, characterized by negative urine culture at the 48th hour.

Moreover, this study has helped us gain more information about the different types of pathogens which cause UTIs and their pattern of susceptibility which may aid in appropriate empirical treatment. These results will be shared with different healthcare institutions to improve the in-practice treatment guidelines so that to lower the morbidity and mortality rate and better care for UTI patients.

Conclusion

Our research work proves that ciprofloxacin is more effective than co-trimoxazole in the treatment of UTIs due to E. Coli. Although, literature suggested growing resistance of E. coli to commonly used antibiotics, we would recommend in vitro studies for antibiotic sensitivity testing before making future recommendations. Also, we didn't consider the adverse effects of the drug under test, so we recommend randomized controlled trial comparing not only efficacy but also the safety of the drugs.

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Authors Contribution

MA: Idea conception, study designing, manuscript writing, and proofreading

SAZK: Data analysis, results and interpretation, manuscript writing, and proofreading

MA: Data collection

SM: Data analysis, results and interpretation

FMK: Data analysis, results and interpretation

SU: Data collection

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