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Therapeutic efficacy and safety of ciprofloxacin and co-trimoxazole combination versus ciprofloxacin in urinary tract infection in Sudan

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ABSTRACT

In Sudan there is no sufficient data about treatment of urinary tract infection and the emerging resistance for ciprofloxacin 500mg BD and the adoption of maximum dose of ciprofloxacin 750mg BD to overcome the resistance. That exposed the patients for more adverse effects. The alternative prescription of the second and third generation cephalosporin are very expensive and there is emerging resistance of cephalosporin by Enterobacteriace bacteria secreted β-lactmase (Sibhghatulla Shaikh,Jamale Fatima&ShaziShakil*et al*, 2015).Therefore, this study was set out to evaluate the efficacy and safety of ciprofloxacin 500mg and TMP-SMX 80/400mg (80 mg trimethoprim and 400 mg sulfamethxazole) versus ciprofloxacin 750mg BD in the management of urinary tract infection . It was prospective, experimental, randomized, parallel-group clinical study, conducted at Elmek Nimer University Hospital, in Shendi. Sudan between August 2019 and August 2020. A total of three hundred (300) patients diagnosed with urinary tract infection were enrolled in this study. They were classified into control group included one hundred and fifty (150) patients received oral ciprofloxacin 750mg BID for four (4) days for patients with uncomplicated UTI and 7 days for patients with complicated UTI . The test group included one hundred and fifty (150) patients received oral combination of ciprofloxacin 500mg and cotrimoxazole (TMP-SMX 80/400mg) BD for the same duration of treatment. The effectiveness endpoint and microbiological eradication rate at the test-of-cure visit in the test group (130/150; 86.7%) were superior to those in the control group (113/150; 75.3%), but with insignificant *P*. value of (0.275) .Clinical-cure rates at the test-of-cure visit were 88% (132/150) for the test group and 77.3% (116/150) for control group with insignificant *P*. value of (0.312). Safety was assessed in the intent□to□treat population and the incidence of drug□related adverse events concerning GIT upset were obtained, the frequencies of nausea 13.3%, heart burn 6.7% and epigastric pain 8% and patients without GIT upset 72% were lower in the test group than in the control group (nausea 24.7%., heart burn 9.3%, epigastric pain 18% and patients

without GIT up set 48%) with significant *P*. value of (0.007)Within two weeks post treatment, relapse of UTI in the test group was less (18 patients) than control group (34 patients) with statistically significant *P*. value of (0.027).Therefore, the findings of this study, which need to be verified in a large multicenter study, suggest that the combination of ciprofloxacin 500mg and co-trimoxazole 80/400mg can be an effective, safe, and affordable therapy, with minimum GIT upsets and low rate of relapse for UTI management , and superior to ciprofloxacin 750mg.

Keywords: Ciprofloxacin, Cotrimoxazole, Combination, Urinary tract infection. **Abbreviations:** UTI, urinary tract infection; TMP-SMX, trimethoprim and sulfamethxazole; BD, twice per day (every twelve hours); CFU, Colony Forming Unite.

INTRODUCTION

Ciprofloxacin is a bactericidal antibiotic of the fluoroquinolone drug class. It inhibits DNA replication by inhibiting bacterial DNA topoisomerase and DNA-gyrase (Tony Thai; Blake H. Salisbury & Patrick M. Zito, 2020). It's particularly more effective against Gram-negative bacteria than against Gram-positive bacteria (Hooper D, 2018).

Ciprofloxacin is approved by Food and Drugs Administration (FDA) of United State (US) for the treatment of urinary tract infections, sexually transmitted infections (gonorrhoea and chancroid), skin, bone and joint infections, prostatitis, typhoid fever, gastrointestinal infections, lower respiratory tract infections, anthrax, plague, and salmonellosis (Thai T, Salisbury BH &Zito PM*et al* 2020). Ciprofloxacin is available in the market as tablet, infusion, eye drops, suspension and ointment (Vidyavathi, M. Srividya&GorantlaA, 2018).

The most frequently reported drug-related adverse events, from trials of all formulations, all dosages, all drug-therapy durations, and for all indications, were nausea (2.5%), diarrhoea (1.6%), abnormal liver function tests (1.3%), vomiting (1%), and skin rash (1%). Other adverse events occurred at rates of <1% tendonitis (Saint F, Gueguen G &Biserte J*et al* 2000).

The central nervous system (CNS) side effects of ciprofloxacin are well-described, and include confusion and paranoid ideation, ataxia and peripheral neuropathy (Abdalla, AhadAbdalla, Sadigg Tsang & Valerie *et al* 2014)

Co-Trimoxazole

The two components, trimethoprim (TMP) and sulphamethoxazole (SMX) work sequentially to inhibit enzyme systems involved in the bacterial synthesis of tetrahydrofolic acid (THF). SMX binds to dihydropteroatesynthetase which catalyses this reaction.TMP binds to bacterial dihydrofolatereductase (in preference to human dihydrofolatereductase), also preventing the formation of THF (D Byron May, David C Hooper &Jennifer Mitty*et al* 2018).

In the late 1960s, the combination of trimethoprim and sulphamethoxazole (co-trimoxazole) was introduced into clinical practice and used to treat many infectious diseases, such as urinary tract infections, respiratory infections, sexually transmitted diseases, Gram-negative sepsis, enteric infections and typhoid fever(E Goldberg& J Bishara*et al* 2011).
The most common adverse reactions to co-trimoxazole are skin eruptions and mild gastrointestinal symptoms, each occurring in up to about 3% of patients. Hematological abnormalities, including thrombocytopenia, leucopenia or agranulocytosis, anemia, eosinophilia or sulphaemoglobinaemia occur in less than 0.5% of adult patients (Wormser, G.P., Keusch, G.T. & Heel, R.C*et al* 1982).

Justification

Three strategies suggested avoiding antibiotics resistance in the management of UTI, by use of combination of antibiotics; vaccine and molecules have antibacterial action. It was expected that treatment of UTI by combination of ciprofloxacin 500mg and co-trimoxazol 80/400 mg BD to reduce the risk of resistance for each drug and the incidence of GIT upset of ciprofloxacin 500 is diminish comparing to high dose 750 mg.

Objective

This study was set out to evaluate the combination of ciprofloxacin 500mg and TMP-SMX 80/400mg

(80trimethoprim and 400 sulfamethxazole) versus ciprofloxacin 750mg BD in the management of urinary tract infection concerning the effectiveness, GIT up set and relapses within two weeks.

Research Hypothesis

The effectiveness of combination ciprofloxacin 500mg and co-trimoxazole 80/400mg in the management of UTI is higher than ciprofloxacin 750mg, with minimum GIT upsets and low rate of relapse.

Subjects and methods

Study population

Patients who presented to the refer clinic and diagnosed with UTI were considered for enrolment in the clinical study. Eligible patients were ≥18 years of age, with clinical signs and symptoms of UTI , including dysuria, burning micturition, suprapubic pain, flank pain, fever ≥38C, nausea, vomiting, positive leukocyte esterase and/or nitrite test.

Exclusion criteria included pregnant, children less than 18 years old, hypersensitivity to sulpha or ciprofloxacin, patients with gastritis, patients on other antibiotic therapy, patient with seizure, patient aged more than 70 years old and patients unwilling to participated in the study.

Study design and data collection:

This was a prospective, experimental, randomized, parallel-group clinical study, conducted at Elmek Nimer University Hospital, in Shendi. Sudan between August 2019 and August 2020. Data was collected by data collection form and the information's were obtained from consultant, physicians, laboratory and patients. Three hundred (300) patients were diagnosed clinically with UTI were classified into two groups. Test group 150 patient were received oral combination of ciprofloxacin 500 mg and co-trimoxazole 80/400 mg BID for 3 days for uncomplicated UTI, 7 days for complicated UTI. Control group 150 patient were received oral ciprofloxacin 750mg BID for 3 days for uncomplicated, and 7 days for complicated UTI (Kalpana Gupta, Thomas M Hooton& Kurt G Naber*et al.*2011).

Patients were assessed at a test-of-cure visit (4 to 8 days post treatment) for microbiological eradication, clinical cure and GIT upset and detection of infection relapse within two weeks post treatment. Effectiveness of drugs was detected by relief all the symptoms (clinical cure) of UTI and bacteriological eradication by investigation of urine by using dipsticks for detection of leukocyte esterase and nitrite after complete the course of treatment. Gastrointestinal upsets were assessed by complaint of patients from nausea, epigastric pain and heart burn. Determination of relapse within two weeks was done by finding of symptoms, signs and repeating urine culture to determine the causes of relapse if it resistance (persistence symptoms) or reinjection (presence of $\geq 10^5$ CFU/ml of new uropathogen not present at baseline).

Microbiologic methods

Clean-catch, midstream urine samples collected at the baseline pre-treatment visit was analyzed by using dipsticks for detection of leukocyte esterase and nitrite. The dipsticks used were Mission Expert manufacturing by ACON laboratories USA. Urine samples were sent for culture. Cled media was used for isolation of bacteria, and Muller Hinton agar media was used for the identification and quantitative determination of uropathogens. Uropathogens were identified to the species level. Uropathogens present at $\geq 10^5$ CFU/ml were tested for susceptibility to five antibiotics, included Ceftriaxone, Ciprofloxacin, Co-trimoxazole, Gentamicin and Co-amoxiclave using stander disc diffusion method. Two types of media and antimicrobials disc used in this study were manufactured by Hi media laboratories India Pvt. L.td.

Statistical analysis

Suitable statistical software such as SPSS V.21 was used for analysis, while appropriate statistical tests were performed to compare results. Results were considered significant, at level of ($P \leq 0.05$). The data were cleaned and checked for consistency before entering it for analysis.

Ethical consideration

1. The study protocol and amendments were approved by Federal Ministry of Health

National Medicines and Poisons Board-Sudan. No: 044667/س أ ق م Date: 12/9/2019,

2. Ethical clearance was also obtained from the National Ribat University- Faculty of Pharmacy and Faculty of Graduates Studies and Scientific Research.

3. It was also approved by research ethics committee of Shendi University in Sudan. Written permission was granted from the administration of Elmek Nimer University Hospital, in Shendi, where study was conducted.

4. It was taking into account the trust and strict confidentiality with respect to patients and information about them, and was scheduled, based on reliable information and reliable source. This research observed human rights stated in international research protocols.

5. Each patient provided verbal informed consent prior to undergoing any study procedures .Names and personal data were completely secured and transferred to codes to keep the privacy of patients' identities

RESULTS

Table 1: Characteristics of the study population.

Gender	**Male**			**Female**				
Percent	(38)12.7%			(262)87.3%				
Age group (Years)	18-28			29-39	40-50	51-61		62-70
Percentage	(48) 16%			(21) 7%	(62) 20.7%	(79)26.3%		(90)30%
Symptoms	Burning micturition	Dysuria		Suprapubic pain	Fever >38º C	Flank pain	Nausea	Vomiting
Percent	(263)87.6%	(167)55.7%		(116)38.7%	(196)65.3%	(216)72%	(114)38%	(23)7.7%
Urine analysis	Positive esterase test	Leukocyte		Positive Nitrite test	Acidic urine pH	Alkali urine pH		
Percent	(300)100%			(214)71.3%	(268)89.3%	(32)10.7%		
Type of UTI:	Uncomplicated UTI			Complicated UTI	P. value			
Percent	(70)23.3%			(230)76.7%	0.000			

Table 2: Urine culture in Cled media and susceptibility test

	Bacterial growth		**No bacterial growth**		
Percentage	(204)68%		(96)32%		
	Ciprofloxacin	**Cotrimoxazole**	**Ceftriaxone**	**Coamoxiclave**	**Gentamycin**
Sensitivity	(151/204)74%	(131/204)64.2%	(94/204)46.1%	(66/204)32.4%	(166/204)81.4%

Resistance	(53/204)26%	204)35.8%	(110/204)53.9%	(138/204)67.6%	(38/204)18.6%

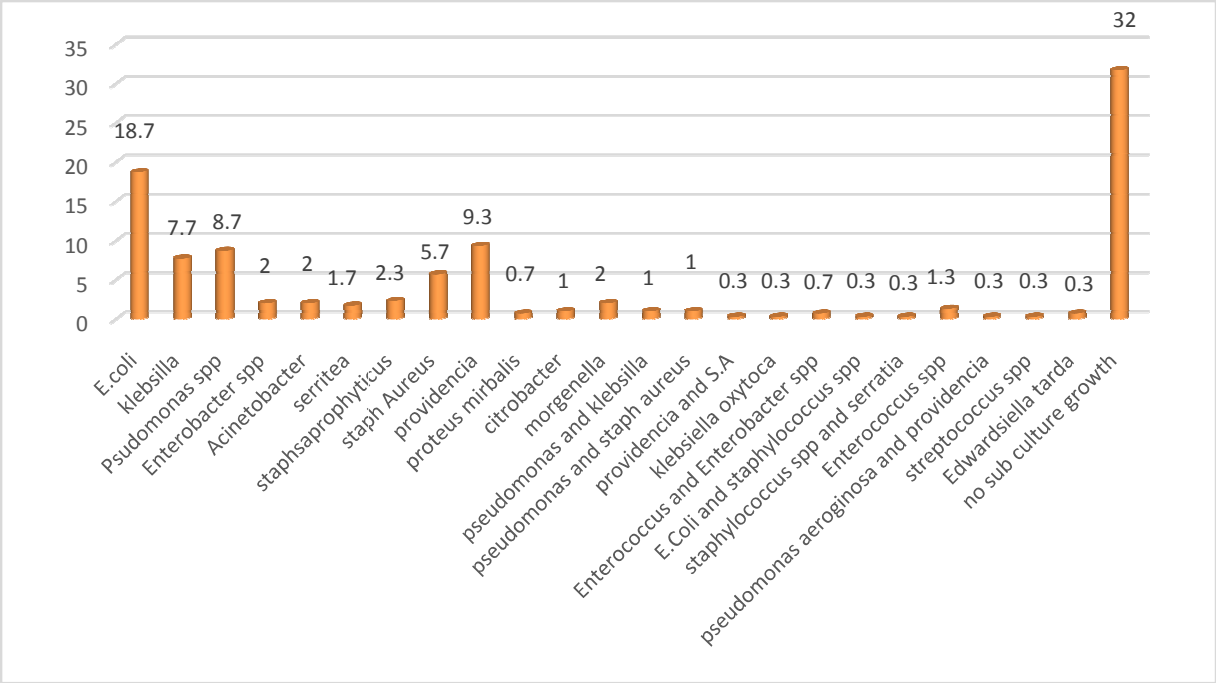

Figure 1: Urine sub culture in Muller Hinton Agar media

Table 3: Efficacy of combination of ciprofloxacin and co-trimoxazole versus ciprofloxacin

Parameter	Control group (Ciprofloxacin 750 mg BD)	Test group (ciprofloxacin 500 + TMP80mg/SMX400mg BD)	*P* .value
Clinical cure	(116)77.3%	(132)88%	0.312
No clinical cure	(34)22.7%	(18)12%	
Bacteriological eradication	(113)75.3%	(130)86.7%	0.275
No bacteriological eradication	(37)24.7%	(20)13.3%	

Table 4: Gastrointestinal upsets in the control and test groups at first test of cure visit post treatment (4, 8 days).

Parameter	Control group (Ciprofloxacin 750 mg BD)	Test group (ciprofloxacin 500 + TMP80mg/SMX400mg BD)	P. value
Nausea	(37)24.7%	(20)13.3%	
Heart burn	(14)9.3%	(10)6.7%	
Epigastric pain	(27)18%	(12)8%	
No GIT up set	(72)48%	(108)72%	0.007

Table 5: Relapse of UTI in the control and test groups within two weeks post treatment.

Parameter	Control group (Ciprofloxacin 750 mg BD)	Test group (ciprofloxacin 500 + TMP80mg/SMX400mg BD)	P. value
Persistence symptoms	(31)20.7%	(13)87%	0.027
Relapse symptoms	(3)2%	(5)3.3%	
Cure	(116)77.3%	(132)88%	

Table 6: Urine re- culture in the control and test groups

Parameter	Control group (Ciprofloxacin 750 mg BD)	Test group (ciprofloxacin 500 + TMP80mg/SMX400mg BD)
Recurrence (Same microorganism)	(34)22.7%	(17)11.3%
Re-infection (New microorganism)	0	(1) 0.7%
Patients not needed urine re culture	(116)77.3%	(132)88.0%

DISCUSSION

The incidence of UTI was decreased during middle age 18-28 years, 29-39 years by 16%, 7% respectively, but raised in older adults 40-50 years, 41-51 years and 61-70 years by 20.7%, 26.3%, 30% respectively, as depicted in table (1) .Similar to other study findings (Sara L Jackson, Edward J Boyko& Delia Scholes*et al* 2004). That was justified as elderly females at post menopause, and elderly males more exposure to prostatitis.

The incidence of UTI was higher in women compared with men across all age groups this similar to other study results (Eriksson I, Gustafson Y &Fagerstrom L*et al*2010)(Caljouw MA, Den Elzen WP & Cools HJ*et al* 2011)(Leonie GM Giesen, Gráinne Cousins & Borislav D Dimitrov*et al* 2010), males were 12.7% (38) and females were 87.3% (262) this indicated a higher prevalence of UTI in females patients compared to male patients due to anatomic and physiological factors such as proximity of the urethra with the vagina and the rectum (Jeff A. Simervill., William C. Maxted, & John J. Pahira *et al* 2005).

Symptoms of UTI were burning micturition 87.7%, dysuria 55.7%, suprapupic pain 38.7%, fever 65.3%, flank pain 72%, nausea 38% and vomiting 7.7%. The patients presented with dysuria, suprapupic pain were less than patients presented with burning micturition, fever, flank pain and nausea.

Diagnosis of UTI performed by nitrite test, 71.3% of samples are positive, so it contrast to study showed that nitrite test positive is 48% (Anith Kumar Mambatta, JayalakshmiJayarajan&Rash meet *al* 2015), and similar to other study findings that showed high nitrite positive test(Juliana Conrad dos Santos, Liliana Portal Weber & Leandro Reus Rodrigues Perez, 2007),nitrite test that confirmed UTI infection (Pezzlo M-1988).28.7% of samples were negatives in spite of diagnosis of UTI this due to gram +ve bacteria, pseudomonas that can't reduce nitrite(Michael J. Bono &Wanda C. Reygaert, 2020) and frequent urinations, which lower the exposure of the microorganisms to nitrate; this can also occur with a diet poor in vegetables which is a source of nitrates (Jeff A. Simervill., William C. Maxted, & John J. Pahira *et al* 2005).

Also leukocyte esterase test was performed to detect presence of white blood cells as indicator for UTI (Pezzlo M-1988), 100% of samples were positive this in contrast to other study results showed that leukocyte test was 23% (Anith Kumar Mambatta, JayalakshmiJayarajan&Rash meet *al* 2015). Similar

to other study findings, that showed high leukocyte test positive (Juliana Conrad dos Santos, Liliana Portal Weber & Leandro Reus Rodrigues Perez, 2007).

Urine PH was acidic by 89.3% this defending mechanism to make media unsuitable for multiplication, 10.7% urine PH is alkali due to presence of phosphorous in urine indicator for perhaps of renal stones(Michael J. Bono &Wanda C. Reygaert, 2020).

Patients with uncomplicated UTI were 23.3% (70) all of them were females with cystitis and pyelonephritis, while patients with complicated UTI were 76.7% (230) included males, catheterized, prostatectomy cases, renal calculi, and diabetes and elder patients. That is mean patients with uncomplicated UTI were less than patients with complicated. And this similar to some study showed complicated UTI is more prevalence than uncomplicated UTI (Laura Vallejo-Torres, MiquelPujol, Evelyn Shaw*et al,* 2018). In contrast to some study showed that uncomplicated increased with age (Anne M. Suskind, Christopher S. Saigal, Janet M. Hanley*et al*, 2016). Statistically this difference was significant P. value of 0.000

Table (2) showed urine culture in Cled media for growth of bacteria to isolation, 68% (204 sample) of samples were grown (> or =$10^{(5)}$ CFU/ml) and 32% (96 sample) weren't grown due to some microorganism can't grow in this media like, Candida albican, atypical bacteria e.g. chlamydia (causative agents of acute urethral syndrome or symptomatic abacteruria) (Jeff A. Simervill., William C. Maxted, & John J. Pahira *et al* 2005), and small number of growth colony (1-2 colony)(<$10^{(5)}$ CFU/ml)which respected insignificant growth. This not similar to other study showed that high no growth samples more than growth samples (Juliana Conrad dos Santos, Liliana Portal Weber & Leandro Reus Rodrigues Perez, 2007).

Invitro susceptibility test was done for growth samples to five antibiotics after isolation and identification of bacteria. Sensitivity to ciprofloxacin represent 74% (151/204 growth samples) and ciprofloxacin resistance is 26% (53/204), that is mean resistance to ciprofloxacin was developed (more than 10% (Richard Cogan, MozellaWilliams & James R Johnson, 2011). This not similar to study showed that ciprofloxacin resistance 50% (Khorvash F, Mostafavizadeh K& Mobasherizadeh S*et al* 2009)

Sensitivity to cotrimoxazole was 64.2% (131/204 sample) and resistance was 35.8% (73/204 sample), in this study cotrimoxazole had activity against pseudomonas in two cases, this similar to study showed activity of cotrimoxazole against one case(Dania Aijaz, ShehnazWasim&FarhanEssa Abdullah, 2015). Also resistance to cotrimoxazole was developed (more than 10%) (Richard Cogan, MozellaWilliams & James R Johnson 2011).

Sensitivity of ceftriaxone was low 46.1% (94/204 sample) and it's resistance was high 53.9%(Richard Cogan, MozellaWilliams & James R Johnson, 2011)(110/204 sample), due to enterobacteraseresist ceftriaxone by secretion of β-lactmase (Sibhghatulla Shaikh, Jamale Fatima&ShaziShakil*et al*, 2015), so ceftriaxone should be avoid in treatment of UTI. This was similar to studies showed ceftriaxone resistance was high (Khorvash F, Mostafavizadeh K& Mobasherizadeh S*et al* 2009)

Sensitivity to coamoxiclave was 32.4% (66/204 sample) and resistance was 67.6% (138/204 sample), this is indication to developing high resistance, so should be avoid in treatment of UTI, this not concomitant to study showed co amoxiclave as first choice as empirical therapy for treatment of UTI (S. P. Barrett, M. A. Savage& M. P. Rebec*et al* 1999) (A. A. van Driel, D. W. Notermans& A. Meima*et al* 2019).

Sensitivity to gentamycin was high 81.4% (166/204 sample) and resistance 18.6% (38/204 sample), so gentamicin is alternative choice for UTI treatment. And this concomitant to other studies (G Beyene&W Tsegaye, 2011) (Chang-Teng, WuHao-YuanLee & Pao-LanTuanet.2016), (Wubalem Desta Seifu & Alemayehu Desalegn Gebissa, 2018)

Figure (1): showed urine subculture in Muller Hinton agar media for identification types of bacteria causing UTI. monoinfection like, E.coli 18.7%, Klebsilla 7.7%, Psudomonasspp 8.7%, Enterobacterspp 2%, Acinetobacter 2%, Serritea 1.7%, Staphsaprophyticus 2.3%, ,staph Aureus 5.7%, Providencia9.3%, proteusmirbalis 0.7%, Citrobacter 1%, Morgenella 2.0%, Enterococcus spp 1.3%, streptococcus spp 0.3%, Edwardsiellatarda 0.3%, mixed infections are pseudomonas and klebsilla 1%, pseudomonas and staph aureus 1%, providence and S.A 0.3%, klebsiellaoxytoca 0.3%, Enterococcus and Enterobacterspp 0.7%, E.Coli and staphylococcus spp 0.3%, staphylococcus spp and serratia 0.3%, pseudomonas aeroginosa and providence 0.3%. This

study was included the variety of causative bacteria, the most isolated bacteria was E coli 18.7% as the similar to other studies (Hamdan Z Hamdan, EmanKubbara & Amar M Adam*et al* 2015)(Omar Bashir Ahmed,2015) (Foxman B, 2014) followed by providence 9.3%, pseudomonas 8.7% and klebsilla 7.7%. This study was showed that new bacteria causing UTI by 9.3% called providence, Previous studies in the Sudan were not identified it (Hamdan Z Hamdan, EmanKubbara & Amar M Adam*et al* 2015) (Omar Bashir Ahmed, 2015). Also this study was showed pseudomonas by high rate 8.7% concomitant to some study (Gordon KA, Ronald N Jones & SENTRY Participant Groups (Europe, Latin America, North America)*et al* 2003), and in contrast to other studies ,which showed low rate of pseudomonas infection 1%nitrite(Michael J. Bono &Wanda C. Reygaert *et al* 2020)(Juliana Conrad dos Santos, Liliana Portal Weber & Leandro Reus Rodrigues Perez, 2007). In the current study the less isolated rate of bacteria (≤1%) are proteus mirbalis, Citrobacter, Enterococcus spp, streptococcus spp, Edwardsiellatarda 0.3% and mixed infections this similar to other studies (Levison ME & Kaye D, 2013)(Fisher JF, Kavanagh K&Sobel JD *et al* 2011)(Jacobsen SM, Stickler DJ & Mobley HL*et al* 2008).

A total of three hundred (300) patients were evaluable to the primary measure of effectiveness by clinical cure and bacteriologic eradication at the end of therapy (4 days to 8 days). Firstly patients were informed about clinical improvement must be start within 48 hours, as in table (3).

Among one hundred and fifty (150) patients were treated with ciprofloxacin 750 mg BD (control group) and assessed to clinical cure, 77.3% (116) of patients were clinically cured,16 patients were poor adherence to the drug due to GIT up set so they continued in the treatment from seven days to ten days (Kalpana Gupta, Thomas M Hooton& Kurt G Naber*et al* 2011)and at end of duration they cured , and 22.7% (34) of patients were not clinically cured due to resistance of bacteria based on urine culture and sensitivity results, also bacteriological eradication was investigated, 75.3% (113) of patients were completed bacteriological eradication, about three patients cured clinically , but still bacteriological eradication not complete because they were diabetic and with mixed infection, and 24.7% (37) weren't completed bacteriological eradication because bacterial resistance to ciprofloxacin. This is similar to study showed that effectiveness of ciprofloxacin was relatively high (J. Boerema, B. Boll& H. Muytjens*et al* 1985), in contrast to other studies showed that effectiveness of ciprofloxacin was very high.(Esposito S, Galante D& Barba D*et al* 1988)(Iravani A, Tice AD& McCarty J*et al* 1995)(Jean L. Fourcroy, Bret Berner& Yu-Kun Chiang*et al* 2005). Also contrast to studies showed that effectiveness of ciprofloxacin was very high compared to TMP/SMX (Dan Rosenbaum, Sylvia Luther& Alex Krist, 2000)(Irving H. Gomolin, Paul F. Siami&Jonathan Reuning Scherer *et al* 2005) (Zalmanovici Trestioreanu A. Green H& Metal 2010)

Among (150) patients were treated by combination of ciprofloxacin 500mg cotrimoxazole80/400mg BD (test group) and evaluated to clinical cure (resolution of symptoms) at test of cure visit post treatment (4, 8 days) 88% (132) were clinically cured, 4 patients were poor adherence to the drug due to dose regimen so they continued in the treatment from seven days to ten days(Kalpana Gupta, Thomas M Hooton& Kurt G Naber*et al* 2011) and 12% (18) of patients were not clinically cured, also these patients were evaluated to bacteriological eradication, 86.7% (130) of patients were completed bacteriological eradication and 13.3% (20) of patients were not completed bacteriological eradication, two patients were improved clinically (resolution of symptoms), but at follow up urine analysis by comber ten strips was observed presence of bacteria lead to continue of treatment course from seven days to ten days based on approved dose duration(Kalpana Gupta, Thomas M Hooton& Kurt G Naber*et al* 2011)and all of them cured from UTI at the end of treatment. one study demonstrated the effectiveness of combination of ciprofloxacin and TMP/SMX and showed that the effectiveness of combination of ciprofloxacin and TMP/SMX was higher than effectiveness of TMP/SMX (Wojciechowski D& Chandran S, 2013).

Overall effectiveness of combination of ciprofloxacin 500mg and TMP80/SMX400mg was high (132 patient clinically cured/130 patient complete bacteriological) compared to effectiveness of ciprofloxacin 750mg (116 patient clinically cured/113 complete bacteriological eradication), but statistically insignificant *P*. value of (0.312) and (0.275) respectively.

Safety was assessed in the intent to treat population and the incidence of drug related adverse events concerning GIT upset were obtained at test of cure visit post treatment (4, 8 days) as appeared in table (4). Patients in control group had nausea 24.7% (37), heart burn 9.3% (14), epigastric pain 18% (27) and patients without GIT upset 48% (72/150), similar to other study showed that GIT up set were significant with ciprofloxacin(J. Boerema, B. Boll& H. Muytjens*et al* 1985), and contrast to other study showed that GIT up set was in frequent .(Esposito S, Galante D& Barba D*et al* 1988).

While patients in test group who had nausea were 13.3% (20), heart burn 6.7% (10), epigastric pain 8% (12) and patients without GIT upset 72% (108/150). To the best of knowledge available, there was no study showed GIT up set of combination ciprofloxacin and TMP/SMX.

So safety regarding to the patients without GIT upset significantly higher in test group (72%) than in the control one, with significant *P.* value of (0.007).

In table (5) patients were evaluated for detection relapse within two weeks post treatment in the control group 20.7% (31) of patients with persistence symptoms (recurrence) due to resistance of bacteria for ciprofloxacin. 2% (3) relapse symptoms after cured due to contaminated source of water, so just 34 patients who needed urine re culture. 77.3% (116/150) of patients with no relapse. This is similar to other studies showed that relapse rate of ciprofloxacin was high (Fox MT, Melia MT& Same RG*et al* 2017)(Nicoletti J, Kuster SP& Sulser T*et al* 2010).

Also patients were assessed to find relapse in test group within two weeks post treatment, 8.7% (13) of patients with persistence symptoms (recurrence). 3.3%(5) relapse symptoms after cured, so 4/5 patients were exposed to the second infection during two weeks with the same microorganism based on re culture of urine result due to contaminated water source and one case infected with new microorganism. 88 %(132) of patients with no relapse.

Relapse of UTI in the test group was less (18 patient) than patients were treated by ciprofloxacin 750 (34 patient), with statistically was significant *P.* value of 0.027

In table (6) urine re-culture of control group 22.7% (34) of patients with the same microorganism (relapse due to resistance called recurrence) with sensitivity to other antimicrobial rather than ciprofloxacin and they were treated depending on result of urine re culture and sensitivity, no reinjection with new microorganism, 77.3% (116) of patients not needed urine re culture and they were respected cured from UTI.

Urine re-culture of test group 11.3% (17) of patients with same microorganism (relapse due to resistance called recurrence) with sensitivity to other antimicrobial rather than ciprofloxacin and TMP/SMX and they were treated depending on result of re culture and sensitivity, reinjection with new microorganism 0.7% (one patient), 88% (132) of patients not needed urine re culture and they were considered cured from UTI

CONCLUSION

The findings of this study, which need to be verified in a large multicenter study, suggest that the combination of ciprofloxacin 500mg and co-trimoxazole 80/400mg in the management of UTI was effective, safe, and affordable therapy with minimum GIT upsets and low rate of relapse, compared to ciprofloxacin 750mg alone.

AUTHOR'S CONTRIBUTIONS

1. Dr. Afaf Ali Abdelrahim: the principal investigator conceived the idea collected the data, interpreted the data generated and wrote the draft of the manuscript.
2. Prof. Abdelwahab Hassan Mohammed: the supervisor of the research
3. Dr. Osama Khder Ahmed: recruited and followed up clinically the participants in the study.
4. Dr. Waseem Sameer Kwami: conducted the laboratory analysis.
5. Dr. Haghamad Allzain: helped interpret the data and provided critical suggestions and comments and edited the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest with any party pertaining to this research.

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