Original Article

Comparison of the effect of co-trimoxazole and co-trimoxazole plus ciprofloxacin in urinary tract infection prophylaxis in kidney transplant patients

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Abstract

Background: Urinary tract infection (UTI) as an important infection in the setting of renal transplantation carries the high mortality and morbidity rate. Thus, the prevention of this infection should receive higher priority. However, bacterial resistance to antibiotics is on the rise, with limited data to guide prophylaxis. The purpose of this study was to compare the effect of sulfamethoxazole-trimethoprim (SMZ/TMP) and SMZ/TMP plus ciprofloxacin for prophylaxis of UTI in renal transplant recipients.

Materials and Methods: In a clinical trial study, 50 patients were included and divided into two groups of 25 using block randomization. Patients in Group I received prophylactic SMZ/TMP and those in Group II received ciprofloxacin plus SMZ/TMP. The incidence of UTI in the two groups at 1, 3, and 6 months after transplantation was evaluated. This study was registered in Iranian Registry of Clinical Trial (IRCT number: IRCT 2015120823743N1).

Results: Of the 61 patients older than 18 years at the time of transplantation, 50 were included. UTI was documented in 8 patients (32%) in Group I and 3 (12%) in Group II ($P = 0.026$). The average time for the development of the first case of infection was the same for both groups ($P = 0.241$), and it was at its maximum in the 1st month. Urinary infections caused by *Escherichia coli*, the dominant strain, were the same in both groups ($P = 0.673$).

Conclusions: Our study shows that the addition of 1 month course of ciprofloxacin lowered the incidence of UTI. More studies are needed to confirm the efficacy of this approach.

Key Words: Ciprofloxacin, co-trimoxazole, kidney transplant, prophylaxis

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Received: 15.12.2015, **Accepted:** 30.01.2016

INTRODUCTION

Urinary tract infection (UTI) as a common infection after renal transplantation has remained a major problem. This rate varies from 30% to 79% between different studies, concerning nearly 60% of bacteremia arising from different transplantation zones.[1] This frequently happens in the early stages after surgery.

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.183669

How to cite this article: Khorvash F, Mortazavi M, Hakamifard A, Ataei B. Comparison of the effect of co-trimoxazole and co-trimoxazole plus ciprofloxacin in urinary tract infection prophylaxis in kidney transplant patients. Adv Biomed Res 2016;5:108.

However, diagnosis becomes more difficult when UTI occurs after being grafted. Moreover, diagnosis might be delayed, potentially leading to bacteremia or pyelonephritis. The clinical manifestations are acute cystitis, pyelonephritis, or sepsis. Previous studies reported a daily prevalence rate of 5–10% for kidney transplant patients from the time that the infected catheter was placed.[2] There are several factors contributing to aggravated risk of UTI in renal transplant patients, such as long-term hemodialysis before graft, female, catheterization time, history of UTI before kidney transplantation,[3] vesicoureteral reflux, diabetes mellitus, intraoperative ureteral stents, old age, and being immunosuppressed.[4]

A broad range of pathogens can cause UTI in this setting. The bacteria causing UTI in immunosuppressed patients are similar to those found in non immunosuppressed ones. The most prominent agent is known as *Escherichia coli*. Furthermore, *Proteus mirabilis* and *Klebsiella pneumonia* are other causes.[2] Any UTI might be detected averagely within 4–7 days.[5,6]

Ciprofloxacin also plays a key role in the treatment of UTI.[7] Given the above facts, appropriate evaluation and starting prophylaxis appear to curtail the mortality risk. However, bacterial resistance to antibiotics is on the rise, and yet there are diverse guidelines concerning prophylaxis. Among these drugs, co-trimoxazole was selected as the drug of choice since it can be effective in simultaneous *Pneumocystis jiroveci* pneumonia. Nevertheless, a number of previous studies reported an increase in microbial resistance to this drug. Considering the appropriate coverage on other strains, this drug is an essential part of prophylaxis protocol in transplant patients. Due to limited information for selection of an appropriate antibiotic as well as the varying reports concerning higher resistance of *E. coli* and other UTI-causing organisms against co-trimoxazole, this study attempted to evaluate the effect of a combined regimen. Ciprofloxacin was the drug of choice in treating of UTI. Previous studies involved this drug in combination with co-trimoxazole leading to a lower risk of this infection. Moreover, literature review suggested that there have been very few studies in Iran focusing on UTI in renal transplant patients treated with combined drugs. In this study, the effect of combination regimen on prophylaxis of UTI in renal transplant patients in Isfahan Transplant Center was evaluated.

MATERIALS AND METHODS

This study was a clinical trial study that performed in Isfahan, Iran. During 1 year since 2014–2015, kidney transplant patients in Transplant Center of Al-Zahra Hospital of Isfahan were enrolled in this study. The inclusion criteria involved kidney transplant patients with age over 18 years, consent to inclusion, lack of recent urinary infection, and lack of glucose 6 phosphate dehydrogenase. The exclusion criteria were inaccessibility to the patient to determine various causes of urinary infection such as death or migration, concurrent use of other antibiotics in the course of investigation, withdrawal from the study, allergic reaction to medications, and drug intolerance. This study was registered in Iranian Registry of Clinical Trial (IRCT number: IRCT 2015120823743N1).

Considering the confidence level of 95% (Z1 – a/2 = 1.96), power of 80% (Z1 – b = 0.84), prevalence of UTI in kidney transplant patients of 50% (given the lack of similar domestic studies) (P = 0.5), and minimum significant difference between the two groups of 0.4, the sample size required for the study for comparison of two proportions was calculated 24 patients in each group using the sample size estimation formula. For greater certainty, however, a total of 25 patients were enrolled in each group. The convenience sampling method was used in this study, and the patients were alternately distributed in the two groups in a block-randomized manner until achieving the required sample size.

Of the 61 patients older than 18 years at the time of transplantation, 50 were included and divided randomly into two groups of 25 patients. Patients in Group I received prophylactic sulfamethoxazole-trimethoprim (SMZ/TMP) and those in Group II received ciprofloxacin plus SMZ/TMP. In Group I, SMZ/TMP was administered with a daily dose of 160/800 mg for 6 months as in standard protocol. In Group II, SMZ/TMP was administered daily for 6 months along with 250 mg ciprofloxacin every 12 h for the first 1 month. The patients were followed at 1, 3, and 6 months after renal transplantation and were treated in case of UTI based on the organism causing the infection.

The criteria for UTI definition included symptoms of cystitis such as dysuria and frequency, or symptoms of pyelonephritis such as fever, tenderness of the transplanted organ, dysuria, and frequency with a positive culture and a colony count of more than 10^5. The routine maintenance regimens for both groups were the same: Tacrolimus, mycophenolate mofetil, and prednisolone. Tacrolimus was administered at the dose which its level in serum reaches to 10–12 ng/ml and with monitoring its level. Prednisolone used for either induction or maintenance and its dosage gradually decreased. Hence, two groups were well-matched.

The peri and post-operative prophylactic antibiotics were cefazolin for both groups until the patient's catheterization and hemovac removed.

The patients and their families were taught to contact the researcher as soon as noticing the clinical symptoms to immediately undertake a remedial action. For patients who enrolled the study, demographic data, reason for renal failure, maintenance therapy before transplantation, type of immunosuppressed regimen, incidence of UTI, urinary infection symptoms, and laboratory findings in the course of investigation were recorded through questionnaires. We used SPSS-22 software (IBM SPSS Statistics) for analysis of data. The Chi-square test (to compare the qualitative and nominal data between the two groups) and *t*-student test (to compare quantitative data between the two groups) were used.

RESULTS

Each of the two groups (Group I: Co-trimoxazole; Group II: Co-trimoxazole plus ciprofloxacin) included 25 patients. There were (36%) 9 females and (64%) 16 males in Group I, and (32%) 8 females and (68%) 17 males in Group II, with the average age of the participants in Group I, 40.32 ± 1.21 years, and that of Group II, 41.08 ± 1.31 years, respectively [Table 1].

The most frequent reason for kidney graft, and cause of kidney failure, in patients of both groups were diabetes mellitus (DM) and hypertension, with no statistically significant differences between the two groups (60%, 15 patients in Group I, and 72%, 18 in Group II, $P = 0.442$). Eight patients (32%) in Group I and 3 (12%) in Group II developed UTI during the research according to the definition criteria ($P = 0.026$). The average time for the development of the first case of these infections was the same for both groups ($P = 0.125$), and it was at its maximum in the first month. Urinary infections caused by *E. coli* species were the same in both groups ($P = 0.673$) and actually, the dominant strain in both groups was that *E. coli* [Table 2].

A higher percentage of patients in Group I (75%) suffered from DM and urinary infection, compared to the Group II.

Table 1: Baseline demographic

Age and gender	Group I (*n*=25)	Group II (*n*=25)	*P*
Age, mean (SD), years	40.32 (1.21)	41.08 (1.31)	0.621
Male/female	16/9	17/8	0.362

SD: Standard deviation

Table 2: Results

ESRD etiology and other results	Group I (*n*=25)	Group II (*n*=25)	*P*
Reason for kidney graft and cause of renal failure			
DM	10	9	0.422
HTN	5	9	
Others	10	7	
Infections			
Yes	8	3	0.026
No	17	22	
The time of developing UTI *n* (%)			
Month 1	5 (62.5)	3 (100)	0.125
Month 3	2 (33.3)	0 (0)	
Month 6	1 (12.5)	0 (0)	
Percentage of isolated organism in patient with UTI *n* (%)			
Escherichia coli	6 (75)	2 (66.7)	0.673
Others	2 (33.3)	1 (33.3)	

DM: Diabetes mellitus, HTN: Hypertension, UTI: Urinary tract infection

DISCUSSION

A major cause of hospitalization and morbidity after renal transplantation is infections, particularly UTI.[2,8,9] Enteric Gram-negative *Bacilli* and *Enterococcus* species are most common,[10] but organisms with resistance have occurred.[11] The incidence is estimated 25% to 45%.[12,13] SMZ/TMP for prophylaxis is suggested for at least 6 months according to the Kidney Disease Improving Global Outcomes guideline in renal transplant patients and other guidelines.[8,14] There are several guidelines that show the importance of prophylaxis against UTIs in these patients, but adequate data are limited, and this issue needs more investigations. One of the important infections in this setting is UTI and correlated with increased mortality.[15-17] In our study, the average time for the development of the first case of infections was the same for both groups, and it was at its maximum in the 1st month that is similar to the study by Golebiewska in 2011 that showed the most percentage of UTIs were diagnosed during the 1st month post transplantation.[18] The predominant isolated agent was *E. coli* (75% Group I and 66.7% Group II); similar to the result of other studies[14,19,20] also in the group of patients with UTI, the incidence of DM was more. It has been shown that SMZ/TMP or ciprofloxacin is effective for prophylaxis although high percentages of uropathogens are resistant to the former.[14,21-25] Fluoroqiunolones are active against many agents and may represent a substitute or in combination for prophylaxis according to other investigations. One of the adverse effects is rising creatinine level in transplanted kidney, so it is rationales that add to the current regimen for a short course as in this study done. In the study by Hibberd *et al.*,[26]

patients received either ciprofloxacin or TMP-SMZ daily for 6 months following transplantation and showed that ciprofloxacin is at least as effective as TMP-SMZ in the prevention of UTI. Although in our study, we used combination regimen and used ciprofloxacin only for 1 month, because the risk of emergence of ciprofloxacin-resistant strains and also the risk of adverse effect of ciprofloxacin in renal transplant patients when use for more duration time. A retrospective study by Wojciechowski *et al*. in 2013[27] also implied that adding ciprofloxacin to SMZ/TMP was more effective for reducing the risk of UTI, which is compatible with our study; however, the two limitations of that study was the first that the dosing regimen of SMZ/TMP (lower doses) which may affect the results in favor of ciprofloxacin, and the second that was a retrospective study. The limitation of our study was the sample size, due to two reasons; first, a load of transplant patients in this center and second, we could not enroll all of the transplant patients in this study because of not meeting inclusion criteria, decline to participate, and other reasons. Up to now, overall, the data for comparing these two drugs are also limited.[26-28] Hence, more studies need to evaluate this concern.

CONCLUSIONS

This clinical trial demonstrated that the addition of 1-month ciprofloxacin to the current regimen, SMZ/TMP, for prophylaxis of UTI in renal transplant patients was associated with a reduced risk of it. As the resistance to current antibiotic prophylaxis regimens increases and according to the significant prevalence of UTI among renal transplant patients and also limited data on urinary infection prophylaxis in this high-risk group of patients about comparing the effect of different antibiotic prophylaxis regimen, the more investigation is needed.

Acknowledgments

We gratefully acknowledge all the academic staff of Infectious Diseases and Nephrology Department of Isfahan University of Medical Sciences.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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