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# High-dose intravenous vitamin C reduces urinary tract infection post-kidney transplantation

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## Abstract

**Background:** Urinary tract infection (UTI) accounts for about half of all post-kidney transplant infections. There is conflicting data regarding vitamin C and UTI prevention. So far, its efficacy has not been studied in renal transplant patients.

**Methods:** Kidney transplant candidates were randomized between vitamin C and placebo arms. In the treatment group, patients received vitamin C infusion at a single dose of 70 mg/kg. In another study arm, only the diluent solution was administered. Data regarding bacteriuria during the first hospitalization after transplantation were recorded.

**Results:** A total of 19 patients were randomized to the placebo ( $n = 10$ ) and vitamin C ( $n = 9$ ) group. The rate of bacteriuria during the first hospitalization after transplantation was significantly lower in the vitamin C group than in the placebo group, 11.1% versus 60%, respectively. ( $P = 0.02$ ).

**Conclusion:** Vitamin C as a safe treatment is a potential prophylactic agent in post kidney transplantation UTI.

**Keywords:** Bacteriuria, Kidney transplantation, Urinary tract infection, Vitamin C

## 1 Background

Urinary tract infection (UTI) is the most common infection after kidney transplantation, which is associated with mortality, morbidity, graft rejection, and graft loss [1]. Bacteriuria and cystitis affect more than 25% of kidney transplant recipients in the first year after transplantation [2]. Given the burden of this infection, finding a solution to prevent it can be conducive. In particular, following the increase in microbial resistance, the effectiveness of antibiotic prophylaxis is reduced. However, non-antibiotic prophylaxis is not affected by this problem. Some non-antibiotic prophylaxis, such as vaginal estrogen in postmenopausal women, probiotics, and vitamin C, has been assessed in studies [3]. The evidence for the effect of vitamin C in reducing UTI episodes is inconsistent

[3]. Especially in healthy women, vitamin C has not been effective enough to be recommended as UTI prophylaxis [4]. In contrast, vitamin C intake in pregnant women at a daily dose of 100 mg has been able to prevent bacteriuria and UTI significantly [5].

Given the available evidence, vitamin C may also be useful as a safe supplement in reducing UTI and post-transplant bacteriuria. Accordingly, one of the purposes of this study was to investigate this issue.

## 2 Method

The reported data in this article are one of the secondary outcomes of a clinical trial. Patients who were candidates for the first kidney transplantation from a deceased donor were included after signing written consent form. The study protocol was according to the Helsinki Declaration and approved by the local ethics committee. Patients in the vitamin C arm received a single-dose parenteral vitamin C (500 mg/5 ml ampoules, DarouPakhsh Pharmaceutical Company,

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Iran) at a dose of 70 mg/kg diluted in 0.45% sodium chloride. The solution was infused within the last hour before transplantation. Patients in the other arm received the same volume of saline solution as a placebo in this period. Supra-physiologic blood concentrations are needed for the effectiveness of vitamin C to achieve primary outcomes of the trial. The half-life of parenteral vitamin C is short, so vitamin C bolus will attain higher plasma levels for only a short period. Transplant recipients from deceased donors in this study were pre-op admitted only a few hours before transplantation surgery. Often, a dialysis session was also performed during these hours. According to vitamin C uptake during dialysis, the time interval between the end of the dialysis session and transplant surgery is selected. At this time, it was possible to inject the mentioned dose of parenteral vitamin C within 1 h. Therefore, the intravenous infusion was selected as the prescribing method during the final hour before surgery. Immunosuppression regimens and prophylaxis of opportunistic infections were similar for the two groups based on the center's protocol. In addition to donors' and recipients' baseline data, allograft function and all information regarding the bacteriuria or crystalluria were also recorded. Data were analyzed using SigmaPlot 12.3 (Systat Software, San Jose, CA). Results are presented as mean  $\pm$  SD or median (minimum–maximum) for normal and non-normal distributed quantitative variables and as number (percent) of patients for nominal variables. The *t* test or Mann–Whitney *U* test was performed to compare normally and non-normally distributed quantitative variables between the two groups of the study, respectively. Qualitative data were compared using the chi-square or Fisher test.  $P < 0.05$  was considered statistically significant.

### 3 Results

A total of 19 patients were randomized to the placebo ( $n=10$ ) and vitamin C ( $n=9$ ) groups. Demographic characteristics were not statistically different between the two groups (Table 1). The rate of bacteriuria during the first hospitalization after transplantation was significantly lower in the vitamin C group than in the placebo group ( $P=0.02$ ). In vitamin C arm, 11.1% of patients had a positive urine culture versus 60% in the placebo arm (Table 2). All patients with bacteriuria received antibiotic treatment according to the antibiogram pattern. Following the administration of high-dose intravenous vitamin C, no evidence of oxalate deposition in tissue biopsies nor crystalluria in urine analysis was observed. Ultrasound results showed no kidney stones during the first three months after transplantation.

**Table 1 Demographic information of transplant recipients**

Characteristic	Vitamin C arm ( $n=9$ )	Placebo arm ( $n=10$ )	<i>P</i>
Age (years)	33.33 $\pm$ 4.59	45.20 $\pm$ 11.03	0.06
Sex (female), <i>n</i> (%)	3 (33.3)	5 (50)	0.65
BMI (Kg/m <sup>2</sup> )	22.10 (15.5–29.4)	21.65 (19.1–25.4)	0.96
Cause of ESKD, <i>n</i> (%)			0.27
Hypertension	2 (22.2)	1 (10.0)	
Diabetes mellitus	2 (22.2)	0	
Glomerulonephritis	2 (22.2)	2 (20.0)	
PKD	0	2 (20.0)	
Drug-induced	0	2 (20.0)	
Other causes	3 (33.3)	3 (30.0)	

BMI body mass index; ESKD end-stage kidney disease; PKD polycystic kidney disease

### 4 Discussion

Reducing the incidence of bacteriuria with or without symptoms in the vitamin C group was one of the secondary outcomes of a double-blind, randomized, controlled trial. The prevalence of bacteriuria in the vitamin C group was considerably lower than in the placebo group. Patients in both groups received trimethoprim/sulfamethoxazole as prophylaxis of *Pneumocystis jiroveci* pneumonia. It is also useful to some extent in the prevention of urinary tract infections [1]. Also, patients in this center receive ceftriaxone as long as they have a urinary catheter. Despite these common antibiotic treatments, the prevalence of bacteriuria during first hospitalization after kidney transplantation was 60% in the placebo group.

UTI accounts for about half of all post-kidney transplant infections [6]. The inhibitory impact of vitamin C on the growth of some pathogens like *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus* has been shown in some studies [7, 8].

The growing rate of antibiotic resistance in urinary tract pathogens has led to the search for non-antibiotic prophylaxis which is not affected by antibiotic resistance [3]. In a study published in 2012 cranberry juice, L-methionine, or both modalities significantly reduced the annual incidence of UTI among kidney transplant recipients with recurrent UTIs compared to the year before the onset of prophylaxis [9]. Information on the administration of a bacterial antigen vaccine for the prevention of UTI is advancing, but this type of treatment has been further studied in non-transplant patients with recurrent UTI [10, 11]. Since these interventions have not been studied in large population, they are not currently recommended [10].

**Table 2 Outcomes comparison between study arms**

Outcome	Vitamin C arm (n = 9)	Placebo arm (n = 10)	P
Bacteriuria during hospitalization, n (%)	1 (11.1)	6 (60.0)	0.02
Concurrent pyuria and bacteriuria, n (%)	1 (11.1)	5 (50)	0.05
Pathogens, n	<i>Escherichia coli</i> (1)	<i>Escherichia coli</i> (3) <i>Klebsiella pneumoniae</i> (2) <i>Enterococcus faecalis</i> (1)	
Hospitalization duration (days)	14 (9–48)	18 (8–32)	0.87

Urinary acidification and production of reactive nitrogen species are proposed mechanisms for the effect of vitamin C on reducing urinary tract infections [4]. Based on in vitro data, nitrite that is produced by bacteria can be reduced to nitric oxide and other nitrogen-reactive intermediates in the presence of vitamin C. These nitrogen intermediates have bactericidal effects [8, 12]. Vitamin C can also prevent biofilm formation on the urethral catheter surface. Besides, at the concentration of 80 to 100 mg/ml, vitamin C exerts an inhibitory effect on a preformed biofilm on the catheters [13]. These desired urinary concentrations can only be achievable by administration of high-dose intravenous vitamin C [14]. On the other hand, in another study, vitamin C could reduce adhesion of uropathogens to the silicone rubber and their colonization in the urine at the dose of 1 g/day for three consecutive days [15].

Some risk factors make the kidney transplant recipients more susceptible to UTI. These risk factors include female gender, older age, pre-transplant history of UTI, urinary reflux or polycystic kidney disease, long duration of urinary catheterization, and delayed allograft function [2, 9]. There was no difference regarding these risk factors between patients in the vitamin C and placebo groups in the present study. For further research, designing clinical trials with large sample size by controlling these risk factors between placebo and vitamin C groups is recommended. It is also suggested to differentiate between asymptomatic bacteriuria and UTI. Besides, recording urine pH at specified intervals may also be useful in the determination of the mechanism of action of vitamin C on bacteriuria and UTI.

## 5 Conclusion

Vitamin C as a safe supplement may be a potential prophylactic agent against post-kidney transplant UTI. However, the dose and duration of therapy should be optimized in future studies.

### Abbreviation

UTI: urinary tract infection.

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### Competing interests

The clinical trial has been encoded IRCT20100111003043N13 in the Iranian registry of clinical trials. Available at: <https://en.irct.ir/search/result?query=IRCT20100111003043N13>

### Authors' contributions

MB contributed to research conception and design, data acquisition, data analysis and interpretation, administrative and technical support, manuscript drafting, and critical revision and finalization of the manuscript. SDK contributed to research conception and design, data acquisition, data analysis and interpretation, administrative and technical support, supervision, manuscript drafting, and critical revision and finalization of the manuscript. AA, NN, and SMG contributed to data acquisition, data analysis and interpretation, administrative and technical support, and critical revision and finalization of the manuscript. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate

All precipitants signed a written consent form. Also, the study protocol was approved by the local ethics committee of Tehran University of Medical Sciences (IR.TUMS.TIPS.REC.1398.007).

### Consent for publication

Not applicable.

### Competing interests

Authors declare no conflict of interest.

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