

Are cranberry capsules effective and safe in preventing urinary tract infections in kidney transplantation? A randomized pilot clinical trial.

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■ ABSTRACT

Introduction: Kidney transplant (KT) recipients are highly susceptible to urinary tract infections (UTIs). Few data are available regarding the effects of cranberry products in KT recipients. **Subjects and methods:** This was a randomized double-blind study comparing daily treatment with a cranberry capsule versus a placebo capsule for 6 months. The study protocol was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee. The study group comprised women undergoing KT for over 1 year, and the exclusion criteria included simultaneous antibiotic UTI prophylaxis. The primary endpoint was UTI occurrence, and the secondary endpoints were the time to first UTI, hospitalization, antibiotic resistance, graft function, immunosuppressive dose changes, and side effects. **Results:** 55 KT women at a single centre were included as follows: 25 were randomized to the cranberry group, and 30 were assigned to the placebo group. During the study period, 16.4% of the participants presented with a UTI. A diagnosis of UTI within the previous year and KT duration, but not cranberry use ($p=0.95$) were independent predictors of UTI. **Discussion:** Cranberry capsules appear to be safe in KT women; however, no clinical efficacy of UTI prophylaxis was demonstrated in this well-designed but underpowered study. Further multicentric and longer trial should be performed to determine cranberry clinical efficacy.

Key-words: Cranberry; Prophylaxis; Kidney Transplantation; Urinary Tract Infection; *Vaccinium macrocarpon*.

■ INTRODUCTION

Urinary tract infections (UTIs) are a critical burden in kidney transplant (KT) recipients¹⁻³. Cranberry, or *Vaccinium macrocarpon*, is a fruit with an extract that is used as traditional UTI prophylaxis. Alongside the apparent benefit of cranberry extract to UTI prevention, there is a clear perception that relevant adverse effects are rare.⁴

However, scarce evidence is available concerning the efficacy and safety of cranberry products in KT patients. We performed a randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of cranberry capsules in women who had received a KT. To our knowledge, this is the first randomized study conducted to assess the potential benefit and safety of cranberry treatment in the prevention of UTIs in KT.

■ SUBJECTS AND METHODS

■ Study design and subjects

This was a randomized, double-blind, placebo-controlled study comparing daily placebo or cranberry capsule administration for a total of 6 months in a Kidney Transplant Unit – Unidade de Transplantação António Pina, Hospital Santa Cruz, Centro Hospitalar Lisboa Ocidental (CHLO). The study protocol and consent form were approved by the Ethics Committee at the CHLO, and research was conducted according to the principles expressed in the Declaration of Helsinki. Study subjects were adult women who had received a KT more than 12 months earlier, had an estimated glomerular filtration rate ≥ 30 mL/min/1.72 m², and had received no other pharmacological prophylaxis treatment during the study. Exclusion criteria included the presence of an indwelling catheter, pregnancy, UTI diagnosis or suspicion of UTI at the time of screening, use of long-term antibiotics or cranberry products, and a known intolerance or allergy to cranberry products.

■ Primary outcome

The primary outcome was UTI occurrence during the study period.

■ Secondary outcomes

The time from randomization to UTI diagnosis, antibiotic resistance profile changes, pharmacological interactions with immunosuppressive drugs, graft function evolution, tolerability, and safety were evaluated.

■ Study product

The pharmaceutical company Xamane[®] manufactured and supplied both the cranberry and placebo capsules. Cranberry capsules were approved and available as over-the-counter medication and each capsule contained 36 mg of A-type proanthocyanidins and 100 mg of ascorbic acid. The placebo capsule consisted of 100 mg of ascorbic acid. Both capsules were indistinguishable and codified to enable double-blinding.

■ Sample size

Estimating that UTI would occur in 30% of patients and based on a previous study by Pagonas *et al.*, we

predicted that a final sample of 140 participants would be required to have 80% power at $p < 0.05$ of detecting a 60% UTI reduction in the cranberry capsule treatment group.⁵

■ Randomization

Using a computer-generated randomization table, subjects were randomized to receive either cranberry or placebo.

■ Collected variables

Socio-demographic characteristics, cause of kidney disease and co-morbidities were recorded. Patients were further characterized according to the induction and maintenance immunosuppression. Patients were divided into high and low immunologic risk groups according to the induction regimen (antithymocyte globulin or basiliximab, respectively). To characterize and compare UTI risk, UTI occurrence during the 12-month period prior to study inclusion was evaluated.

■ Follow-up and adherence

All patients underwent follow-up clinic visits and laboratory evaluations, including urinalysis, urine cultures, and serum levels of immunosuppressive medication, according to the KT centre clinical practice protocols.

■ Statistical analysis

All statistical analyses were performed using SPSS[®] version 21.0 software, according to the intention-to-treat principle and a two-sided $p < 0.05$ value was considered statistically significant. Baseline socio-demographic and clinical characteristics were summarized using descriptive statistics. According to the nature and distribution of data, variables were compared using the chi-square test, Fisher's exact test, Student's t-test, and Mann-Whitney U test, as appropriate. Time to the first episode of infection was plotted as a Kaplan-Meier curve, and differences were assessed using the log rank test. Multivariate logistic regression analysis was used to evaluate independent risk factors associated with UTI during the study period.

RESULTS

Fifty-five women with KT were recruited: 25 were randomized to receive cranberry capsules, and 30 were randomized to receive placebo capsules. The different number of randomized patients in each group is the result of a randomization table designed for a larger sample and the inability to reach a larger sample size.

Socio-demographic variables and clinical characteristics

Table 1 lists the baseline socio-demographic and clinical characteristics of the included patients. A global analysis indicated a relatively lower proportion of diabetic patients (12.7%) and patients with previous urological disorders that led to chronic kidney disease (CKD) (7.2%).

Urinary tract infections

Previous 12-month period and risk factors

Twenty-four cases of UTI were diagnosed in 17 patients (30.9%). The leading causative microorganism responsible for UTI in this population was *Escherichia coli* (n = 22, 91.7%). A significant difference in cephalosporin resistance was identified, and the resistance was greater in the cranberry group. Table 2 lists UTI occurrence and microbiological data in both groups. Age, race, diabetes mellitus, previous urological disorder, date of KT, maintenance regimen, and graft function were not associated with a higher UTI incidence.

Urinary tract infections during the study

During the 6-month study period, 9 patients (16.4%) presented with 10 UTIs, 4 patients in the cranberry group (16%) and 5 patients in the placebo group (16.7%) (p = 0.95). Antimicrobial resistance

Table 1

Baseline characteristics of patients in cranberry and placebo groups.

Variables	Cranberry group	Placebo group	P value
Age (mean ± SD)	51.8 (± 12.2)	52.3 (± 9.0)	0.86
Non-white (number; percentage)	5 (25%)	2 (6.7%)	0.14
Diabetes mellitus (number; percentage)	2 (8%)	5 (16.7%)	0.34
Urological disorder as cause for CKD (number; percentage)	2 (8%)	2 (6.7%)	0.85
Months after KT (mean ± SD)	86.2 (± 63.1)	87.1 (± 48.5)	0.96
High immunologic risk induction regimen (number; percentage)	8 (32%)	12 (40%)	0.54
CNI-based maintenance regimen	19 (76%)	25 (83.3%)	0.50
mTORi-based maintenance regimen	6 (24%)	5 (16.7%)	0.50
Serum creatinine (mg/dL) (mean ± SD)	1.20 (± 0.42)	1.09 (± 0.30)	0.27
eGFR (mL/min/1.73 m ²) (mean ± SD)	61.2 (± 20.6)	63.9 (± 20.9)	0.63

CNI – calcineurin inhibitors; mTORi – mTOR inhibitors.

Table 2

Urinary tract infections in the previous 12-month period.

	Cranberry group	Placebo group	P value
Number of infections / number of affected patients	14 / 9	10 / 8	0.46
Isolated microorganisms			
<i>Escherichia coli</i> (number/%)	13 (93%)	9 (90%)	NS
<i>Enterococcus faecium</i> (number/%)	1 (7%)	0	
<i>Staphylococcus epidermidis</i> (number/%)	0	1 (10%)	
Antibiotic resistances identified per patient			
Amoxicillin-clavulanate resistance (number/%)	3 (33.3%)	1 (12.5%)	0.31
Cephalosporin resistance (number/%)	4 (44.4%)	0	0.03
Quinolones resistance (number/%)	6 (66.7%)	2 (25%)	0.15
Trimethoprim/Sulfamethoxazole resistance (number/%)	7 (77.8%)	5 (62.5%)	0.49
ESBL strain (number/%)	1 (11.1%)	0	0.53

ESBL – Extended spectrum beta-lactamase-producing bacteria

Table 3

UTI during the study period – microbiological characteristics and need for hospitalization

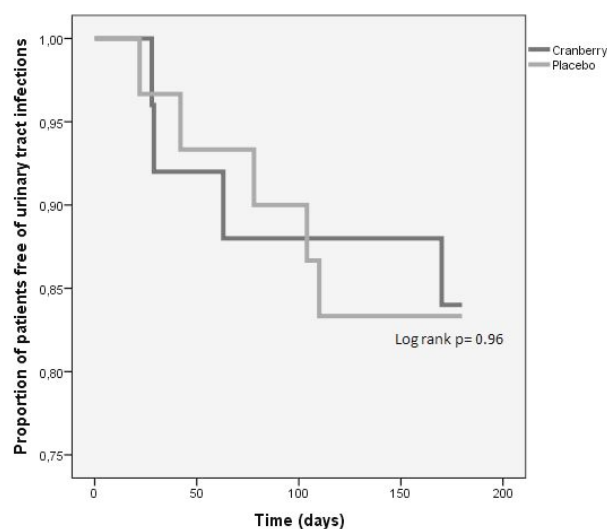
	Cranberry group	Placebo group	P value
Number of infections / number of affected patients	4 / 4	6 / 5	0.95
Isolated microorganisms			
<i>Escherichia coli</i> (number/%)	4 (100%)	4 (66.6%)	
<i>Klebsiella pneumoniae</i> (number/%)	0	1 (16.7%)	
<i>Proteus mirabilis</i> (number/%)	0	1 (16.7%)	
Antibiotic resistances identified per patient			
Amoxicillin-clavulanate resistance (number/%)	2 (50%)	1 (20%)	0.34
Cephalosporin resistance (number/%)	1 (25%)	0	0.17
Quinolones resistance (number/%)	3 (75%)	2 (40%)	0.29
Trimethoprim/Sulfamethoxazole resistance (number/%)	3 (75%)	3 (60%)	0.64
ESBL strain (number/%)	1 (25%)	0	0.24
Hospitalizations cause of UTI			
Number of hospitalized patients	1 (4%)	2 (6.7%)	0.67

rates of identified bacteria and hospitalizations due to UTI are presented in Table 3. The only factors associated with UTI during the study period were a diagnosis of UTI in the previous 12 months ($p = 0.019$) and KT duration ($p = 0.012$). After adjusting for age, diabetes mellitus diagnosis, and graft function, KT duration ($p = 0.021$; ExpB 1.02, 95% CI 1.003–1.035) and prior UTI ($p = 0.028$; ExpB 7.25, 95% CI 1.22–43.1) persisted as predictors of UTI occurrence during the study period. There was no difference in the risk of

developing UTI between the groups after adjusting for KT duration and prior UTI ($p = 0.62$). After study inclusion, the global median time until UTI diagnosis was 63 days (IQ range 28.5–107 days), with no difference detected between the groups ($p = 0.97$). A Kaplan-Meier plot of UTI incidence showed a similar infection rate according to time (log-rank test $p = 0.96$), as noted in Figure 1. Cox regression analysis confirmed that KT duration and prior UTI were predictors for UTI during the study period ($p = 0.009$ and $p = 0.015$, respectively).

Figure 1

Kaplan-Meier survival analysis – time to first urinary tract infection and proportion of patients free of UTI



■ Immunosuppression interference

Patients exhibited adequate therapeutic levels of immunosuppressants in the blood, and immunosuppressant doses were adjusted during the study due to levels under or over the therapeutic goal in 8 patients (5 in cranberry group and 3 in placebo group).

■ Graft function and side effects

During the study period, there was a global mean serum creatinine decrease of -0.06 ± 0.16 mg/dL, which was not related to the intervention ($p = 0.25$) or to UTI occurrence ($p = 0.20$). No patient death, urinary tract obstruction, or graft loss was found in either group of patients. Four patients presented with adverse events, and one patient in the cranberry group abandoned the study due to disturbing epigastralgiias. No serious adverse events or hospitalizations (due to causes other than UTI) occurred in either group.

■ DISCUSSION

■ Tract infections in kidney transplant patients

UTI is a common occurrence in the general population and is associated with considerable clinical and socio-economic consequences.⁶ In patients who have undergone KT, UTI incidence is much higher, and the associated clinical and economic issues are exacerbated.^{7,8}

Different immunosuppressive medications have been associated with different UTI rates in some studies.⁹ Contrary to these findings, the current study did not show such a finding.

■ Cranberry characteristics and potential benefits and harms

The efficacy of cranberry treatment as UTI prophylaxis is based on its effect on bacterial adherence in epithelial cells, primarily in the urinary tract. This action is essentially preventive and has no effect on displacing bacteria already attached to epithelial cells or interfering with the bacterial life cycle. Therefore, cranberry treatment can be used only for UTI prevention and not as a cure.¹⁰ Adherence to mucosal surfaces is a prerequisite for the development of most mammalian infections and is facilitated by fimbriae, which enable bacteria to resist cleansing mechanisms and overcome nutrient deprivation.^{11,12} Only a cranberry component, A-type proanthocyanidins (ATP), was capable of inhibiting P-fimbriae, which is primarily present in *Escherichia coli*.¹³ The evaluation of urinary antibacterial adhesion in *in vitro* and *in vivo* models revealed a significant reduction in bacterial adherence at an ATP dose of 36 mg or higher (efficacy steadily increased until the dose reached 108 mg).¹⁴ Other studies reported the inhibition of adherence and flagellum-mediated motility, and the potentiation of antibiotic activity for a wide range of microorganisms. Importantly, the efficacy of ATP against bacteria is independent of the bacterial antibiotic resistance profile.^{15,16}

Another mechanism of action of cranberry treatment for UTI prophylaxis is based on its effects on the colonic and vaginal tracts. ATP binds to pathogenic *Escherichia* isolates in these locations and inhibits bacterial adhesion prior to further introduction into the urinary tract. As a consequence, ATP influences bacterial selection in these tracts to favour the survival of non-adherent, less pathogenic strains.¹⁵

Clinical studies have reported variable clinical effects associated with the use of cranberry products for UTI prophylaxis.^{17,18} A Cochrane renal group presented a meta-analysis followed by successive updates regarding the efficacy of cranberry products for UTI prophylaxis. The most recent updated Cochrane review included 24 studies, with a total of 4,473 patients. The comparison arms consisted of placebo, no treatment, water, methenamine hippurate, antibiotics, or lactobacillus. Overall, cranberry products were not associated with an increased benefit in the general population or in any of the subgroups. The quality of studies was considered good, but most of the studies were too small to enable a significant difference to be detected.¹⁷ The drawbacks of these reviews are that most studies did not report the amount of the active ingredient and there was a lack of uniformity regarding the intervention, including differences in cranberry formulation, dosing regimen, and duration of the intervention. Again, no KT recipients were included, reflecting a lack of studies in this population. A large number of dropouts and withdrawals (up to 55%) was detected in cranberry juice trials, which was attributed to the reduced lower palatability/acceptability of the cranberry juice.¹⁹

The newer capsule and tablet formulations of cranberry extract have been evaluated and comparison studies revealed equivalent efficacy as for juice. Furthermore, the capsule formulation is more convenient, is less expensive and overcomes compliance issues.⁴

■ Urinary tract infection prophylaxis in patients with a kidney transplant

UTI management remains a widely studied topic in the field of kidney transplantation. Contrary to findings in the general population, no conclusive data are available on antibiotic or non-antibiotic prophylaxis modalities in KT patients. Retrospective data concerning this subject demonstrate that antibiotic prophylaxis decreased UTI occurrence and hospitalization rates. However, long-term results and prospective trials addressing a loss of efficacy and an enhanced risk of antimicrobial resistance are lacking.²⁰ The only published study on UTI prophylaxis in KT patients with cranberry products was a retrospective trial that included 82 KT recipients with frequent UTI. Compared with placebo, cranberry juice was associated with a significant reduction in the annual incidence of UTI by 63.9% ($p < 0.001$).⁵

The current study is the first randomized double-blind placebo controlled trial to evaluate the efficacy of cranberry treatment as UTI prophylaxis in KT recipients. We decided to include only female KT due to the increased susceptibility to UTI in females.^{1,7,21,22} The use of a cranberry capsule in this study provided a uniform method of distributing the product. Additionally, the use of a capsule made it possible to use a similar placebo capsule to achieve double blindness. Regarding primary and secondary endpoints, treatment with cranberry was not associated with fewer UTI events or an increased time to develop the first UTI, and we found no differences in microbiological profiles.

Immunosuppressive therapy interference and graft function were not affected by treatment with cranberry. These particular topics were addressed for the first time in the current study, as no previously published studies evaluated the potential effects of cranberry in a KT setting.

■ Limitations

The main limitations of this trial are the small group size and short follow-up, rendering this study underpowered to detect a difference between the effects of cranberry and placebo. UTI rates were lower in the current study than those assumed in the original power calculations. We propose that the patients included in the current study represent a lower-risk sub-group, as diabetes mellitus prevalence was low, current urological disorders were absent, and graft function was normal.

Given the previous 12-month UTI incidence observed, we would have required 76 participants per group to have 80% power of detecting a difference at $p = 0.05$ at 12 months.

In an attempt to exclude potential effects of concomitant antibiotic use and to eliminate potential bias, we decided to exclude patients with a history of frequent UTIs who were receiving chronic antibiotic therapy. Thus, we excluded patients who would benefit more from additional preventive measures and who present with a higher event incidence.

Another explanation for the lower efficacy is the cranberry dosage used in this study, which may have been insufficient for prophylaxis in this specific population. Studies have demonstrated that a minimum dose of 36 mg of ATP is needed for UTI prophylaxis; however,

efficacy is dose-dependent, suggesting that higher doses can be more protective.²³

Ascorbic acid (AA) is an essential micronutrient that is naturally present in foods, and high levels are present in cranberry. In the current study, it was present in both the cranberry and placebo capsules at the same dose (100 mg)^{16,24} One of the reasons for the use of AA is the stabilization of cranberry extract. Additionally, other studies evaluating cranberry juices vs placebo also included AA in both products.^{25,26} However, AA has been suggested to prevent UTI in experimental studies by pH-dependent and pH-independent mechanisms.^{27,28} We speculate that AA consumption in both groups could lead to a global reduction in UTI incidence.

■ CONCLUSION

We investigated the ability of cranberry to reduce UTI incidence in KT patients, an understudied population. In addition to the absence of clinical efficacy of UTI prophylaxis, this study indicates that treatment with cranberry capsules can be a simple and safe approach in KT care. Additional larger and longer studies should be performed.

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■ DISCLOSURE

Xamane® supplied the placebo and cranberry capsules. Xamane® had no role in the design; methods; subject recruitment; data collection, analysis, and interpretation; decision to submit the manuscript for publication; or preparation of the manuscript.

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Tiago Assis Pereira participated in the study design and patient recruitment and wrote the manuscript;

Raquel Fernandes participated in the database development, data collection, and analysis; Artur Mendes led the statistical analysis; the nurses helped with patient recruitment, compliance, and verification of side effects; Cristina Toscano coordinated the microbiological surveillance; Tânia Laranjeira, Ana Mirco, and Fátima Falcão coordinated the capsule supply, monitored adherence, and registered side effects; Domingos Machado provided central assistance with the development of study protocols and project coordination; André Weigert led the study concept, design, and coordination and funding acquisition efforts and participated in manuscript revision; and the other authors participated in the study design, patient recruitment, and manuscript revision.

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure of potential conflicts of interest: none declared

Abbreviations:

Kidney Transplant – KT
Urinary Tract Infection – UTI
Centro Hospitalar Lisboa Ocidental – CHLO
Chronic Kidney Disease – CKD
A-type proanthocyanidins – ATP
Trimethoprim/sulfamethoxazole – TMP/SMZ
Ascorbic acid – AA

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