ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20230799

Antibiotic versus cranberry in the treatment of uncomplicated urinary infection: a randomized controlled trial

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SUMMARY

OBJECTIVE: This study was designed to determine the effect of cranberry extract used in patients with single urinary tract infections.

METHODS: Patients with simple-type urinary tract infections were divided into two groups. Treatment with fosfomycin or cranberry tablet was started. On days 1, 3, and 7 of the treatment, whether there was a decrease in the complaints was evaluated with a Likert-type scale. The recovery status of urinary tract infections and the well-being of patients were compared via antibiotic and cranberry groups.

RESULTS: After the treatment, the leukocyte levels of the cranberry users were at the same level as those of the other group, and the rate of well-being and the portion of patients that reported to be "very well" on days 3 and 7 in the cranberry group was significantly higher compared with the fosfomycin group ($p<0.05$).

CONCLUSION: Considering the results of this study, it was determined that the patient's complaints decreased from day 3 and their well-being increased with the use of cranberry only. Specifically, on day 7, the well-being of the cranberry group was higher than that of the fosfomycin group. For this reason, cranberry is a favorable alternative to antibiotics in uncomplicated and simple urinary tract infections.

KEYWORDS: Cranberry. Fosfomycin. Urinary tract infection.

INTRODUCTION

Urinary tract infection (UTI), which is reported to be the second most common infection worldwide, is a condition that presents itself with alarming symptoms in women, and most of these women are treated with antibiotics[1,2]. Moreover, UTI may cause significant morbidity because of high recurrence rates and antibiotic resistance. In patients who frequently come down with UTI, this condition adversely affects gastrointestinal flora, liver, and kidney metabolism. Also, it causes a significant burden on the economies of countries.

The uropathogenic *Escherichia coli* (UPEC) pathogroup of *Escherichia coli*, which is classified into several pathogenicity groups according to particular virulence characteristics, is the most common causative agent of uncomplicated UTIs. *Staphylococcus saprophyticus*, a Gram-positive bacterium, is the second most common cause of uncomplicated UTI. Besides, *Klebsiella pneumonia* and *Proteus mirabilis* are other less common causes of UTIs. However, the Gram-positive bacteria *Enterococcus* and *Staphylococcus* have been more commonly detected as the causes of UTIs than studied previously. Due to these factors, UTIs will remain widespread[3].

Due to increased antibiotic resistance resulting from the widespread overuse and abuse of antibiotics such as beta-lactams, trimethoprim-sulfamethoxazole, and quinolones in many different countries around the world, for routine treatment of bacterial infections, including UTIs, it is observed that interest in non-antibiotic therapies for the management of these conditions is growing[4]. As a result, scientists are constantly searching for new strategies and therapeutic alternatives to antibiotics for the prophylaxis and treatment of UTIs. Cranberry, a fruit widely recommended for the prophylaxis of UTIs in traditional medicine, has emerged as a new alternative to antibiotics against UTIs and has become a new research subject in this field[5].

Cranberry fruit (*Vaccinium macrocarpon*) is a distinctive source of polyphenols such as flavonoids and phenolic acids, which have high antioxidant properties and are known to positively affect health[2]. It is available in cranberry, tablet/capsule, dried fruit, and cranberry juice/extract. Proanthocyanidin (PAC) with type A bindings or metabolites is considered the active ingredient in cranberries. It is stated that cranberry extract can be a potential alternative to antibiotics in treating acute UTIs

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 26, 2023. Accepted on August 27, 2023.

without complication, particularly considering factors such as the reduction of the ability of *E. coli* by preventing it from adhering to the bladder uroepithelium[6].

There is still uncertainty about the effectiveness of non-antibiotic therapies for UTIs, and relevant studies on cranberries and other new combined formulations are going on. However, it is observed that most studies have evaluated the efficacy of cranberry extract in recurrent UTIs. Still, only a few studies evaluate its effectiveness in acute UTIs[7]. Therefore, in this study, we aimed to determine the effect of using cranberry extract in uncomplicated UTIs (that involve only the urinary tract and bladder, not kidneys).

METHODS

Ethics approval and consent to participate

This study was approved by the Local Ethics Committee and the Medicines and Medical Devices Agency (2021-514-212-7/E-E-85521274-000-1364973). All study participants gave written and verbal consent to the study. This study was carried out in accordance with the Declaration of Helsinki principles.

Study sample

This study was conducted as a prospective, randomized study. All male and female patients who presented to the Emergency Department (ED) and the Internal Medicine Outpatient Clinic between January 2022 and February 2022 were included in the study. The study was conducted with 170 patients (n=85 cranberry and n=85 fosfomycin).

This study included willing male patients and female patients who were not pregnant or suspected to have a pregnancy, who met the inclusion criteria of being aged 18 years or older, presenting to the ED and Internal Medicine outpatient clinic with complaints of dysuria, frequent urination, and nausea, having no known chronic kidney disease, and having only elevated leukocyte levels in the urine test results without pathology in blood tests.

Methods for data collection

Patients who accepted to participate in the study were divided into either the treatment group or the control group according to the order of arrival (1:1). Patients in Group 1 were given 7 cranberry tablets in one pack of cranberries "36 PAC available in 1 tablet (Ocean Cranberry, Orzax)" to be used once a day (QD). Patients in Group 2 were prescribed two sachets of fosfomycin every 3 days (TID). The study was completed with 170 patients, with 85 patients in each group. The researchers collected study data through in-person and telephone interviews. Each data collection method took about 10 min for the participants to complete.

Availability of data and materials

This study was retrospectively registered on clinicaltrials.gov with the trial number NCT05260554.

Follow-up of patients

The variables of age, gender, and admission symptoms were recorded for the patients included in the study, and treatment of their choice was initiated. The tests for leukocyte count, C-reactive protein (CRP), and kidney functions were suggested among patients with complaints increasing in severity during treatment. The patient was excluded from the study when pathology was identified and switched to the appropriate treatment. During admission, patients were asked to rate how serious their complaints were using the Likert-type verbal psychometric scale[8] (Table 1). Patients were called for a control examination (or queried on the phone) on days 3 and 7 of their treatment to question and record their well-being status. This study determined how quickly the patients' complaints recovered based on their treatment methods. The efficacy of the treatment was compared considering the leukocyte values in the results of control urine tests performed for the patients who completed the treatment. The results were evaluated based on the thesis that cranberry extract can be an excellent alternative to antibiotics in treating simple, uncomplicated urinary infections.

Statistical analysis

Study data were analyzed with SPSS 28.0. The mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used for the descriptive statistics of the data. The chi-square analysis was used to examine the distributions between groups. The Kolmogorov-Smirnov test was used for measuring the distribution of variables. The Mann-Whitney U test was used for analyzing independent quantitative data. The Wilcoxon test was used for analyzing dependent quantitative data.

Table 1. Likert-type scale.

1 point	So bad
2 point	Bad
3 point	Not bad
4 point	Well
5 point	Very well

RESULTS

Of all patients in the study, 117 (68.8%) were females, 53 (31.2%) were males, and their average age was 53.4 (13.6) years (Table 2). In the fosfomycin group, the leukocyte count before treatment was significantly higher ($p<0.05$) than in the cranberry group. After treatment, the leukocyte counts of the subjects who took cranberry were identical to those of the other group (Table 2).

The complaint of nausea during treatment was observed not to change significantly in either group ($p>0.05$) (Table 2). The patients were asked whether their complaints were decreasing daily, and it was determined that, while the number of participants who gave 4 points to the question became higher in the group using fosfomycin, most of the participants using cranberry gave 5 points. In the cranberry group, the rate of participants reported to be "well" and "very well" on day 3 and the rate of those said to be "very well" on day 7 were significantly ($p<0.05$) higher compared with the fosfomycin group (Figure 1).

DISCUSSION

In this study, most patients with UTIs were postmenopausal women. The literature has reported that uterine muscles weaken, and vaginal Lactobacilli decreases in menopausal women due to reduced estrogen. Moreover, it has been reported that UTI pathogens, particularly Enterobacteriaceae, are responsible for colonization because of the increased pH levels. It is also

Table 2. Demographic characteristics of patients, types of treatment applied, laboratory results, and well-being.

		Fosfomycin		Cranberry		p
		Mean±SD n-%	Median	Mean±SD n-%	Median	
Age (years)		51.9±13.2	54.0	55.0±14.0	57.0	0.182[m]
Gender	F	59–69.4%		58–68.2%		0.868[X²]
	M	26–30.6%		27–31.8%		
Leukocyte						
Before treatment (BT)		19.6±6.8	18.0	16.5±5.1	16.0	**0.001**[m]
Post-treatment (PT)		8.6±14.8	2.0	7.4±13.9	2.0	0.558[m]
BT/PT		-11.0±14.9	-14.0	-9.1±14.5	-12.0	0.080[m]
Intragroup change p.		**0.000**[W]		**0.000**[W]		
Well-being						
Day 1	So bad	1–1.2%		1–1.2%		**0.045**[X²]
	Bad	24–28.2%		13–15.3%		
	Not bad	53–62.4%		57–67.1%		
	Well	7–8.2%		14–16.5%		
Day 3	So bad	1–1.2%		0–0.0%		**0.038**[X²]
	Bad	17–20.0%		9–10.6%		
	Not bad	20–23.5%		15–17.6%		
	Well	40–47.1%		46–54.1%		
	Very well	7–8.2%		15–17.6%		
Day 7	So bad	7–8.2%		1–1.2%		**0.003**[X²]
	Bad	11–12.9%		10–11.8%		
	Not bad	4–4.7%		10–11.8%		
	Well	45–52.9%		27–31.8%		
	Very well	18–21.2%		37–43.5%		
Nausea	No	39–45.9%		33–38.8%		0.352[X²]
	Yes	46–54.1%		52–61.2%		

[m]Mann-Whitney U test; [w]Wilcoxon test; [X²]chi-square test. Statistically significant values are indicated in bold.

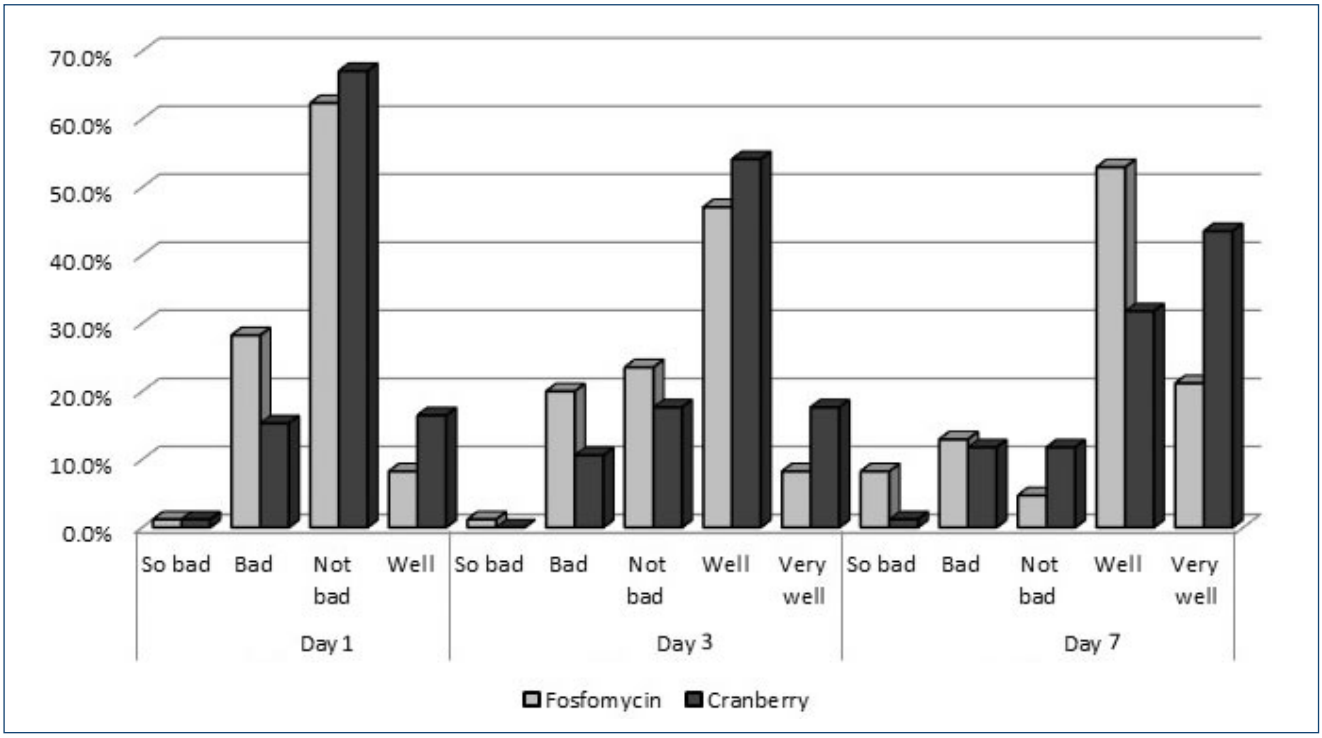

Figure 1. Distribution of well-being by days.

emphasized that UTIs may recur every 6–12 months after menopause[9]. Considering these facts, postmenopausal women have a higher risk of developing UTIs. For this reason, they form a higher portion of the study sample in this study.

The most significant characteristic of *E. coli* in UTI pathogenesis is its adherence to the host tissue with pili and fimbriae[10]. Type-1 fimbria and P-fimbria are the most important types of these structures. Following adhesion, uropathogenic are protected against micturition. Antibiotics and urinary antiseptics are often used in treatment. Cranberry fruit content includes water (88%), organic acids (including salicylate), fructose, vitamin C, flavonoids, *anthocyanidins,* catechins, and tri-terpenoids[11]. PAC in cranberry is considered the primary active ingredient and prevents Type-I and P-fimbriae adhesion of *E. coli* to the urogenital mucosa[12].

Cranberry is not an antimicrobial but can contribute to treatment as it indirectly inhibits bacterial adherence. It was demonstrated in a study by Sobota that, among the subjects who used diluted and concentrated cranberry juice, those who consumed the concentrate had less bacterial adhesion[13]. Faggian et al., observed that an increase in PAC polymers inhibited bacterial adhesion at the same rate[14]. This study used cranberry extract, which is high in PAC content (36 PAC=514 mg cranberry). When a comparison was made between the leukocyte levels in the urinalysis before and after the treatment, similar results were compared with the group using fosfomycin. This finding suggests that UTIs can be treated without using antibiotics.

In a study conducted to determine the effect of cranberry extract on antibiotic use in women with acute uncomplicated UTI, Gbinigie et al., concluded that it is possible to conduct randomized controlled studies with cranberry extract and that it has no side effects for patients[5].

In a study by Maki et al., the subjects were divided into two groups to receive cranberry juice and a placebo drink. As a result of the study, Maki et al., found that UTI episodes were reduced by 39% in subjects using cranberry juice[15]. Hess et al., compared cranberry tablets to placebo tablets in patients with neurogenic bladder[16]. There was a 60% decrease in UTIs in patients using cranberry tablets. Regardless of the form of cranberry used, successful results can be achieved with cranberry in treating UTIs.

Cranberries (*V. macrocarpon*) are generally cultivated in countries that have warm climates. As it is a cheap and easily accessible fruit, it can be thought that encouraging patients to consume cranberry will not be complicated by emphasizing its therapeutic effects. Furthermore, it has been demonstrated that cranberries protect against dental, gastrointestinal, and cancer and have antiviral activity[17-19].

In a study by Terris et al., it was determined that the risk of renal oxalate stones increases in patients using cranberry tablets

which has been attributed to vitamin C supplements in tablet form[20]. Additionally, patients with high levels of calcium oxalate had a familial history of kidney stones. Considering this result, it cannot be claimed that the cranberry tablet is good regarding the risk of developing kidney oxalate stones. However, there are several predisposing factors for this condition. Nevertheless, patients using cranberry extract should be monitored for renal stones.

CONCLUSION

This study determined that cranberry extract positively impacts the patient's well-being. Based on the data obtained, successful results can be achieved in treating UTIs using cranberries.

Limitations

The study population was limited to patients who presented to a single center between specific dates and were diagnosed with an acute UTI. Moreover, patients who had unresolved complaints were excluded from the study. Prolonging the treatment period could have been considered in that group of patients. However, further investigation was performed, and antibiotic therapy was started for those patients so as not to affect the study format. In addition, long-term follow-up of patients using cranberry could not be performed. It could not be followed whether side effects developed or not.

ACKNOWLEDGMENTS

The authors thank Orzax Company for their support. This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHORS' CONTRIBUTIONS

OG: Conceptualization, Data curation, Methodology, Software, Writing – original draft. **SS:** Conceptualization, Formal Analysis, Supervision, Writing – original draft. **ÖT:** Resources, Software, Supervision. **NMH:** Resources, Software, Supervision, Writing – review & editing. **DVK:** Validation, Supervision, Writing – review & editing.

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