Does cranberry have a role in catheter-associated urinary tract infections?

Dominique Thomas, BS[1]; Matthew Rutman, MD[2]; Kimberly Cooper, MD[2]; Andrew Abrams, MPH[3]; Julia Finkelstein, MD[2]; Bilal Chughtai, MD[1]

[1]Department of Urology, Weill Cornell Medical College/New York Presbyterian Hospital, New York, NY, United States; [2]Deptartment of Urology, Columbia University Medical Centre/New York Presbyterian Hospital, New York, NY, United States; [3]Diana H. Jones Innovative Senior Centre, Brooklyn NY, United States

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Abstract

Introduction: Catheter-associated urinary tract infections (CA-UTIs) are a prevalent and costly condition, with very few therapeutic options. We sought to evaluate the efficacy of an oral cranberry supplement on CA-UTIs over a six-month period.

Methods: Subjects with long-term indwelling catheters and recurrent symptomatic CA-UTIs were enrolled to take a once-daily oral cranberry supplement with 36 mg of the active ingredient proanthocyanidin (PACs). Primary outcome was reducing the number of symptomatic CA-UTIs. This was defined by ≥10^3 (cfu)/mL of ≥1 bacterial species in a single catheter urine specimen and signs and symptoms compatible with CA-UTI. Secondary outcomes included bacterial counts and resistance patterns to antibiotics.

Results: Thirty-four patients were enrolled in the trial; 22 patients (mean age 77.22 years, 77.27% were men) completed the study. Cranberry was effective in reducing the number of symptomatic CA-UTIs in all patients (n=22). Resistance to antibiotics was reduced by 28%. Furthermore, colony counts were reduced by 58.65%. No subjects had adverse events while taking cranberry.

Conclusions: The cranberry supplement reduced the number of symptomatic CA-UTIs, antibiotic resistances, and major causative organisms in this cohort. Larger, placebo-controlled studies are needed to further define the role of cranberry in CA-UTIs.

Introduction

Catheter-associated urinary tract infections (CA-UTIs) are a major public health issue. In the U.S., these infections account for approximately 36% of healthcare-related infections.[1] This leads to a large economic burden on the patient, provider, and healthcare system. Despite many proposed interventions to alleviate this, CA-UTI rates have still remained high.[2] When patients are catheterized for more than seven days, 10–50% will develop a CA-UTI.[3]

Short of early removal of the catheter, there has been no further intervention to reduce rates of CA-UTIs. Thus, the search for an alternative treatment is of the utmost significance. Interestingly, herbal products have been used to treat UTIs for centuries.[4] In particular, cranberry, in its many forms, has been used for the prevention and treatment of UTIs.[5] The active components in cranberry, known as proanthocyanidins (PACs), are large, condensed tannin molecules with A-type linkages exhibiting strong bacterial anti-adhesion activity.[6] These compounds prevent bacterial adhesion to the bladder wall, thereby preventing infection.[6] There are no studies on the efficacy of cranberry for those with CA-UTIs. We present the results of a proof of concept study evaluating the efficacy and safety of a cranberry supplement on CA-UTIs.

Methods

The study was conducted at two tertiary outpatient facilities and was approved by the Food and Drug Administration (FDA) and Institutional Review Board (IRB).

Patient selection

Subjects with indwelling catheters who had two documented symptomatic CA-UTIs over six months were included. For the purposes of this study, a symptomatic CA-UTI was defined by ≥10^3 (cfu)/mL of ≥1 bacterial species in a single catheter urine specimen[7] and symptoms compatible with CA-UTI, including new onset of fever, rigors, altered mental status, malaise, or lethargy with no other identified cause; hematuria; pelvic pain; or dysuria.[7] If patients developed a CA-UTI at any time during the study, they were treated using an appropriate course of antibiotics based on the sensitivity of their urine culture. Furthermore, the most prevalent isolated organisms were identified for each culture.

All subjects had to be at least 18 years of age. Subjects were not able to tolerate surgery or perform intermittent catheterization (Table 1). All catheters used in the study

were standard latex catheters. No antiseptic catheters were used in this study. Subjects were excluded from the study if they had previous allergic reaction to cranberry-containing products, were taking Warfarin or chronic antibiotics, and/or were performing daily bladder irrigation.

Intervention

Eligible subjects took one capsule of cranberry daily manufactured by Pharmatoka® for six consecutive months. This capsule contains 36 mg of total cranberry extracted from juice (*Vaccinium Macrocarpon Aiton*) proanthocyanidins (PACs-A and -B types together) as measured using the BL-DMAC method.[8] All subjects took the cranberry supplement at bedtime to avoid the alkaline tide of meals, which could negatively affect the efficacy of cranberry. At each monthly visit, urine culture, urinalysis, and symptoms of a CA-UTI were assessed. Catheters were also changed at these visits. Subjects were assessed to ensure there were no other exposures to antibiotics.

Power calculation

This is a pre/post-study, with the rate of UTIs in the prospectively treated patients being compared to the rate of CA-UTIs in the six months prior to treatment (as determined by chart review). We recognize that this is a biased comparison due to the different UTI ascertainment methodologies in the two time periods (i.e., prospective identification vs. prior chart review). Therefore, the primary intent was to estimate the CA-UTI proportion in the prospectively treated cohort. This study was designed to screen for an early indication of efficacy, rather than a definitive demonstration of cranberry efficacy. For this study, assuming an absolute reduction in the number of symptomatic CA-UTIs by 20% and with a type I error of 0.10, a power of 0.80, 95% of confidence intervals, the total sample size required to achieve these objectives is at least 20 subjects. With an attrition rate of 10%, 22 subjects would be required.

Table 1. Baseline characteristics and demographics of subjects enrolled in the pilot study

Characteristic/demographic*	Mean results†
Age, mean±SD	77.22 ±10.00 years
Sex, n (%)	
Male	17 (77.27)
Female	5(22.72)
Common comorbidities, n (%)	
Hypertension	10 (45.45)
Diabetes mellitus	5 (22.72)
Chronic renal failure	3 (13.64)
Congestive health failure	5 (22.72)
Stroke	5 (22.72)
Myocardial infarction	1 (4.55)
Charlson Age-Comorbidities Index (CACI)	
Mean	4.909
Min	2
Max	10
Relative risk of death, mean	7.331
Reasons for catheterization in males (n=17)	
Benign prostatic hyperplasia	12 (71%)
Neurogenic bladder	5 (29%)
Reasons for catheterization in females (n=5)	
Detrusor acontractility	3 (60%)

*Characteristics/demographics: The main patient characteristics we were interested in were reported, such as age, sex, and CACI. †All values are reported as a mean (average) unless stated otherwise.

Statistical analysis

Given this is a proof of concept study, all data collected was analyzed by descriptive statistics. Events and percentages were presented for patient demographics and comorbidities. Mean and standard deviation were calculated for age. All analyses were performed in Stata Version 13.0 (StataCorp, College Station, TX, U.S.).

Results

A total of 34 subjects were recruited for the study, and of these, 22 subjects completed the study (see Fig. 1 for reasons of attrition). The mean age was 77.22 years old (range 56–90) (Table 1). Most, 77.27% (n=17) were males and 22.73% (n=22) were females. The Charlson Age-Comorbidities Index (CACI) mean score was 4.909. Table 2 shows the baseline characteristics for study subjects.

At baseline, the mean number of antibiotic resistance for the major causative organisms was 2.579 1.774 (Table 2). Fig. 2 show the specific antibiotic resistances from baseline throughout the six months the patients were in the study. At six-month followup, the mean number of antibiotic resistance for the major causative organisms had reduced to 1.857±1.215. This is an overall reduction by 28% while on the cranberry capsule.

All subjects at baseline had an average of 1.318±0.716 major causative bacterial organisms in their urine cultures. At the end of the trial, this was reduced to 0.545±0.739. This represents an overall reduction by 58.65% in bacterial organisms found in the study subjects' urine cultures (Table 2).

For the subjects in this study, at baseline their urinalysis showed a mean value of 51.944±41.886 WBC. At the end of the trial, subjects' urinalysis showed a mean WBC of 27.363±14.778 (Table 2).

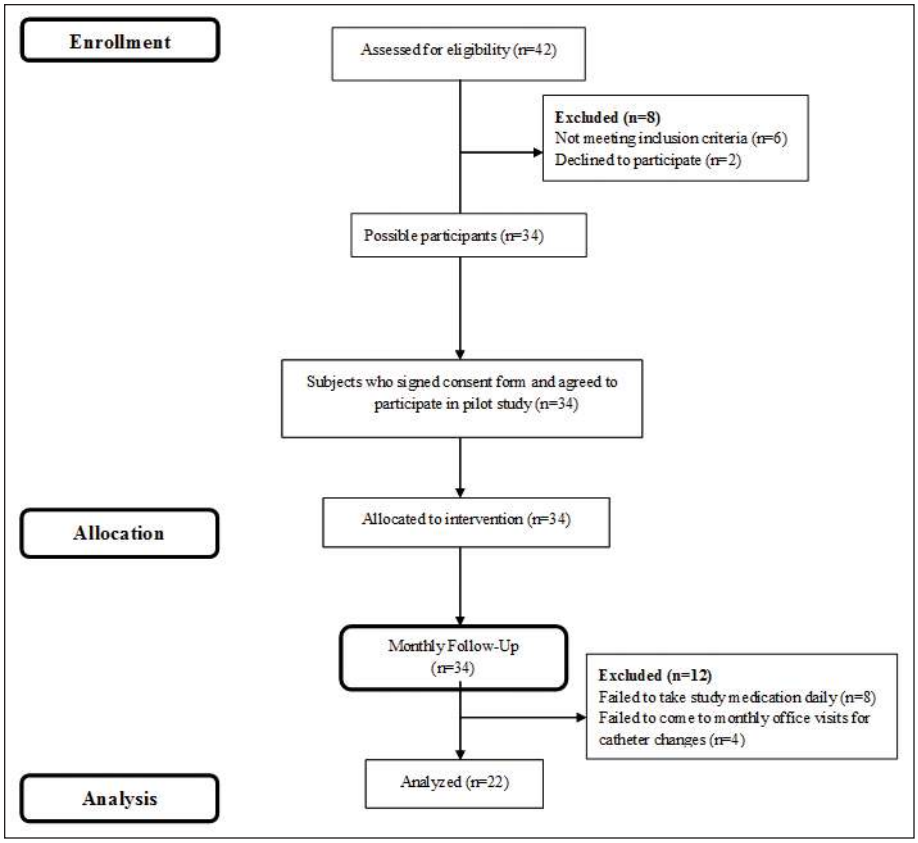

Fig. 1. Study enrollment and intervention allocation process. More than one criterion could apply to each individual. Participants received daily synthesized cranberry extract nutraceutical. Adhering to the protocol indicated taking the daily nutraceutical for six months and attending monthly physician visits for urine culture/urinalysis.

Discussion

This is the first study evaluating the use of a cranberry supplement in CA-UITs. While using this intervention during the six-month trial, no subject presented with symptomatic CA-UTIs. The PACs present in cranberry are thought to inhibit P-fimbriated *E. coli* and other uropathogens from adhering to uroepithetial cells in the urinary tract.[9,10]

Over six months, there was 28% reduction in all antibiotic resistance and a 58.65% reduction in all major causative organisms. There was overall reduction in both the antibiotic resistance and the major causative organisms present in our subjects' urine cultures. This may be due to change in bacterial flora or the decrease use in antibiotics, which thereby reduced the resistant strains.

There have been very few other agents used to reduce CA-UTIs. Methenamine hippurate has been studied for use in both bacteriuria and symptomatic CA-UTIs and has shown some benefit in preventing symptomatic CA-UTIs in patients without any renal tract abnormalities (relative risk [RR] 0.24; 95% confidence interval [CI] 0.07–0.89), as well as bacteriuria (RR 0.56; 95% CI 0.37–0.83);[11] however, patients with a history of renal tract abnormalities were at greater risk for symptomatic UTIs (RR 1.54; 95% CI 0.38–6.20) and bacteriuria (RR 1.29; 95% CI 0.54–3.07).[11] This treatment was only evaluated for one week, therefore, it is difficult to extrapolate data for longer time periods. The overall effectiveness of this intervention remains unclear.

Long-term antibiotic prophylaxis has been used in patients with CA-UTIs.[12] Wazait et al assessed the use of prophylactic antibiotics in patients with and without existing bacteriuria.[12] A total of 48 patients were enrolled. Within a two-week time period, three patients were diagnosed with a CA-UTI. Despite being on a 48-hour course of ciprofloxacin, the incidence of CA-UTI did not decrease.

Almost all the data on CA-UTIs has been on novel catheter systems, such as silver-impregnated or antimicrobial catheters; however, the use of these catheters has not decreased the incidence of symptomatic CA-UTI rates.

Our study was limited by a lack of a formal control group and thus did not compare the efficacy of this intervention juxtaposed to other treatment options. The investigators and the patients involved in this study were aware of the treatment allocation. This may have introduced bias as to which patients would be offered the cranberry. We had a sample size of 22 subjects completing the full study due to attrition and not adhering to the intervention guideline (i.e., not taking the cranberry supplement daily). This was likely due to this population being older and sicker. Another limitation was using subjects as their own historic controls when comparing results.

Table 2. Comparison of patient urine culture and urinalysis results from baseline throughout six-month study period

Urine culture*/urinalysis results	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Average number of antibiotic resistance	2.579	2.4	2.625	2.181	2.667	2.625	1.857
WBC U/A	51.944	55.211	46.333	32.75	46.867	36.857	27.363
Average number of major causative organisms	1.318	1.091	1.181	0.910	1.000	1.045	0.545
Nitrite†	Negative	Negative	Negative	Negative	Negative	Negative	Negative

*Urine culture/urinalysis results: We selected a few important components from our patients' urine cultures and urinalysis and reported them here. All values are reported as a mean (averages) unless stated otherwise. †Nitrite: This value is reported as a binary negative or positive. WBC U/A: white blood cell urinalysis.

Despite these limitations, our study is the first of its kind to use cranberry for prevention of a costly and common problem. Further, no study has long-term six-month data on preventing CA-UTIs. The effect of cranberry was durable during the study period. Further, cranberry was well-tolerated with no unexpected adverse events or allergies.

Conclusion

In conclusion, after taking a cranberry supplement, no subjects presented with symptomatic CA-UTIs during the study period. Further, antibiotic resistances and patterns of major causative organisms decreased. This proof of concept study clearly demonstrates cranberry may be beneficial for this vulnerable and costly condition. There is an urgent need for larger, placebo-controlled trials.

Competing interests: The authors report no competing personal or financial interests.

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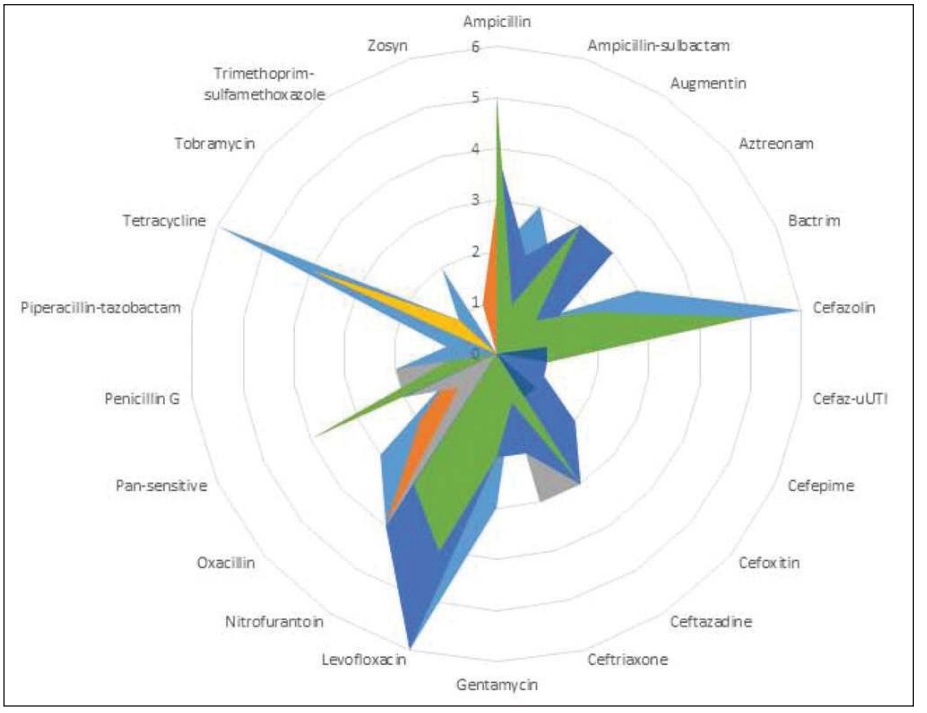

Fig. 2. Radar scatterplot of the number of antibiotic resistances at baseline to six months while on a cranberry supplement. This figure represents the number of antibiotic resistances across the study period from Month 0 until the end of the trial at Month 6. On the outside axis, the names of the specific antibiotics are labelled. A value in this case indicates a major causative organism found in the patient's urine culture/urinalysis has resistance to the specific antibiotic. The y-axis represents the number of resistances. The larger the shaded area, the more antibiotic resistance; the smaller the shaded area, the less amount of antibiotic resistance.

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Correspondence: Dr. Bilal Chughtai, Department of Urology, Weill Cornell Medical College/New York Presbyterian Hospital, New York, NY, United States; bic9008@med.cornell.edu