PILOT RANDOMIZED CONTROLLED DOSING STUDY OF CRANBERRY CAPSULES FOR REDUCTION OF BACTERIURIA PLUS PYURIA IN FEMALE NURSING HOME RESIDENTS

To the Editor: Cranberry products are a nonantimicrobial method for prevention of urinary tract infection (UTI). Cranberry proanthocyanidin (PAC), a type of condensed tannin, is the active ingredient in cranberry that inhibits adherence of P-fimbriated *Escherichia coli* to uroepithelial cells.[1,2] Previous cranberry studies for UTI prevention yielded conflicting results, probably because of variability of PAC dose and clinical populations studied.[3,4] In a clinical trial of 300 mL of cranberry juice beverage daily (36 mg PAC), older women (mean age 78.5) had 58% lower odds of having bacteriuria and pyuria than controls,[5] but nursing home residents have difficulty ingesting the volume of juice necessary to prevent bacteriuria. Cranberry capsules are feasible to administer to nursing home residents, but their efficacy has not been demonstrated.[6] In vitro, 36–108 mg of PAC is efficacious at inhibiting bacterial adherence to uroepithelial cells,[7] but the most efficacious dose for older nursing home residents has not been identified. The goal of this study was to identify the optimal dose of cranberry capsules that reduced the incidence of bacteriuria plus pyuria over 1 month.

METHODS

This study was a pilot double-blind, randomized, placebo-controlled trial of three cranberry capsules (108 mg PAC), two cranberry capsules and one placebo capsule (72 mg PAC), one cranberry capsule and two placebo capsules (36 mg PAC), and three placebo capsules daily for 30 days. The primary outcome was episodes of bacteriuria and pyuria at 7, 14, 21, and 28 days of cranberry capsule treatment. Participants were stratified according to presence or absence of baseline bacteriuria, with 20 participants randomized according to stratum to each arm of the study.

The manufacturer donated cranberry and placebo capsules. Urine cultures and urinalyses were collected at baseline and then weekly for 4 weeks (total 5 specimens). No additional follow-up was performed after the completion of cranberry capsule treatment. Bacteriuria was defined as more than 100,000 colony forming units (cfu) per mL of any bacteria. Pyuria was defined as any white blood cells seen on microscopic urinalysis.[5] Inclusion criteria were female; history of UTI; aged 65 and older; long-term residence; and English speaking. Exclusion criteria were total incontinence, warfarin therapy,[8] <4 weeks residence, chronic indwelling catheter, terminal prognosis, antibiotic therapy, kidney stones, dialysis, cranberry therapy, and cranberry allergy. The Yale Human Investigation Committee approved this study. Eligible residents or surrogates provided written consent. SAS 9.22 (SAS Institute, Inc., Cary, NC) statistical software was used to analyze the data.

RESULTS

One thousand nine hundred twenty-nine residents in 11 homes were screened; 1,381 did not meet inclusion criteria (no history of UTI n = 665, 48.2%; male n = 479, 34.7%; short-term rehabilitation n = 163, 11.8%; non-English speaking n = 38, 2.8%; aged <65 n = 36, 2.6%). Of 548 remaining residents, 308 met exclusion criteria (totally incontinent n = 104, 33.8%; warfarin use n = 72, 23.4%; residence <4 weeks n = 31, 10.1%; chronic indwelling catheter n = 23, 7.5%; discharged n = 20, 6.5%; terminal n = 16, 5.2%; antibiotic therapy n = 14, 4.5%; kidney stones n = 9, 2.9%; cranberry therapy n = 7, 2.3%; administrative decision n = 6, 1.9%; dialysis n = 5, 1.6%; cranberry allergy n = 1, 0.3%), and 240 were eligible; 90 residents consented (37.5% consent rate) and 80 enrolled (10 participants met an exclusion criterion before enrollment). Demographic characteristics of the 80 participants were 98% white (n = 78), mean age 89.2 ± 7, and mean number of comorbidities 4.1 ± 1.7. Most participants were totally dependent in bathing (54%) and had some bowel (67%) and bladder (76%) incontinence. Of 80 baseline urine cultures, one had no growth, eight had less than 100,000 cfu/mL, 41 had more than 100,000 cfu/mL, and 30 had mixed flora (≥ 3 organisms). On baseline urine culture, the placebo and one- and three-capsule groups each had 10 of 20 participants with more than 100,000 cfu/mL, and the two-capsule group had 11 of 20 participants with more than 100,000 cfu/mL. Of 80 baseline urinalyses requested, 73 were obtained: 11 had no pyuria, and 62 had pyuria. Of 320 urine specimens that

Table 1. Cross-Classification of Cranberry Capsule Dose and Presence of Bacteriuria Plus Pyuria

Number of Cranberry Capsules	*Escherichia Coli* Bacteriuria Plus Pyuria n (%)	Other Bacteriuria Plus Pyuria[a] n (%)	Not Growth[b] n (%)	Total n (%)
0	33 (43.4)	5 (6.6)	38 (50.0)	76
1	29 (40.3)	4 (5.6)	39 (54.2)	72
2	23 (29.9)	10 (13.0)	44 (57.1)	77
3	25 (34.3)	12 (16.4)	36 (49.3)	73
Total	110	31	157	298[c]

[a]Other bacteriuria plus any white blood cells (WBCs) is >100,000 colony forming units per mL of a pathogen other than *E. coli* plus any WBCs. For no cranberry capsules, 3 were *Proteus* and 2 were *Klebsiella* species. For one cranberry capsule, 1 was *Proteus* and 3 were *Klebsiella* species. For two cranberry capsules, 2 were *Proteus* species, 1 *Enterococcus*, 4 beta-hemolytic Streptococci, 2 *viridans* Streptococci, and 1 *Morganella morganii*. For three cranberry capsules, 4 were *Klebsiella*, 3 *Enterococcus*, 4 *Citrobacter freundii*, and 1 coagulase-negative *Staphylococcus*.

[b]Not growth includes no growth, growth <100,000, growth >100,000 but no WBCs, and mixed flora. Of 157 no growth, 19 were no growth, 23 were <100,000, 4 were growth >100,000 but no WBCs, and 111 were mixed flora.

[c]There were 22 missing urine culture or urinalysis of the 320 total expected samples.

should have been collected, 302 (94%) urine cultures and 294 (92%) urinalyses were obtained. Results of bacteriuria and pyuria according to cranberry capsule group are provided in Table 1. These results represent four weekly follow-up urine samples obtained per participant while consuming cranberry capsules.

DISCUSSION

This study showed a dose-dependent trend toward decrease in bacteriuria plus pyuria, particularly with *E. coli,* in female nursing home residents ingesting cranberry capsules over 1 month. Previous studies in older patients were conducted using cranberry juice,[5,9] and studies of cranberry capsules are lacking. In this study, *E. coli* bacteriuria was reduced, which is consistent with the mechanism of PAC,[7] but bacteriuria with other pathogens did not show this same pattern of results. *E. coli* accounts for approximately 50% of uropathogens in nursing home residents,[10] and reduction in bacteriuria may reduce treatment for UTI. Because the effect of two and three capsules was comparable and to reduce capsule burden, further investigation of two cranberry capsules daily in nursing home residents is warranted to determine whether the reduction of *E. coli* bacteriuria is sustained over a longer period of time and whether it affect clinical outcomes related to UTI (e.g., hospitalization, antibiotic therapy for UTI).

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COMPARISON OF CHRONIC KIDNEY DISEASE (CKD) EPIDEMIOLOGY FORMULA WITH OTHER CALCULATED CREATININE FORMULAS FOR THE DETERMINATION OF CKD IN COGNITIVELY INTACT AND IMPAIRED ELDERLY OUTPATIENTS

To the Editor: Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 for three or more months. The prevalence of CKD increases with advancing age.[1] Because serum creatinine is not an accurate measure for estimating renal function in elderly adults, creatinine clearance or GFR is used to assess CKD. The criterion standard methods for measuring GFR are based upon injection of a radioactive contrast agent such as iodothalamate or using a substance such as inulin. This method is impractical in regular clinical practice and is not cost effective, so calculated creatinine formulas are used instead. Various formulas for estimating the GFR such as the Cockroft-Gault adjusted for body surface area (CG/BSA), Modified Diet in Renal Disease (MDRD), Wright, and Mayo Clinic formulas have been suggested for calculating GFR from serum creatinine concentration.[2–5] A new formula to estimate GFR from serum creatinine called the chronic kidney disease epidemi-