Effect of Cranberry Capsules on Bacteriuria plus Pyuria among Older Women in Nursing Homes: A Randomized Clinical Trial

BACKGROUND:

- Bacteriuria and pyuria happens often in older patients who are living in a nursing home. Non-antimicrobial prevention is preferred in these patients and all patients but it is understudied and evidence is controversial both in this population and in the general population

OBJECTIVE

- To test the effect of 2 oral cranberry capsules once a day on presence of bacteriuria plus pyuria among women residing in nursing homes

METHODS

- **Design**: Double-blind, randomized, placebo-controlled efficacy trial with stratification. Duration: 360 days with surveillance over 365 days
- **Inclusion criteria**: Female, long-term care residents, English speaking, and 65 years or older
- **Exclusion criteria**: Patients not expected to be in the nursing home for at least 1 month (i.e., short-term rehabilitation, pending discharge, terminal life expectancy <1 month), patients taking chronic suppressive antibiotic or anti-infective (i.e., mandelamine) therapy for recurrent UTI, patients undergoing dialysis for end-stage renal disease patients unable to produce a baseline clean catch urine specimen, patients receiving warfarin therapy, which could cause an interaction with cranberry juice, patients with a history of nephrolithiasis because cranberry products may increase the risk of nephrolithiasis, presence of an indwelling bladder catheter, an allergy to cranberry products, patients currently getting treatment with cranberry products, and nursing home residence for less than 4 weeks.
- **Primary outcome measure**: Presence of bacteriuria (i.e., at least 10^5 colony-forming units [CFUs] per milliliter of 1 or 2 microorganisms in urine culture) plus pyuria (i.e., any number of white blood cells on urinalysis) assessed every 2 months over the 1-year study surveillance
- **Secondary outcome measures**: symptomatic urinary tract infection (UTI), all-cause death, all-cause hospitalization, all multidrug antibiotic–resistant organisms, antibiotics administered for suspected UTI, and total antimicrobial administration
- 92 patients in the treatment group received two oral cranberry capsules (each capsule containing 36 mg of the active ingredient proanthocyanidin which is equivalent to 20 ounces of cranberry juice). 93 patients in the control group were administered placebo once daily.
- Power 80% with an alpha level of 0.05 was calculated to be sufficient for 90 patients per group
- Data handling method was intent-to-treat

RESULTS

- There were 147 patients out of 185 that completed the study. 33 participants died. Twenty participants, 9 in the treatment group and 11 in the control group, became incontinent prior to the first outcome assessment and were unable to provide any of the scheduled urine specimens. Over the course of the study, 45 participants stopped taking the capsules, 24 in the treatment and 21 in the control groups, for the following reasons: patient refusal (N=21), transitioned to hospice care (N=19), started on warfarin which was an early termination event (N=4), and family refusal (N=1).
- **Primary outcome measure**: There was no significant difference in percentage of urine specimens that met the outcome of bacteriuria plus pyuria over 12 months of surveillance between groups. The overall unadjusted results showed rates of 25.5% [95% CI 18.6, 33.9]

vs 29.5% [95% CI 22.2, 37.9]) in treatment versus control groups, respectively. The adjusted analysis, accounting for missing data and pre-specified covariates, showed no significant difference between the treatment and control groups (29.1% vs. 29.0%; OR 1.01, 95% CI 0.61,1.66; p=0.984).

- **Secondary outcome measures**: There were no significant differences in rates of death (17 vs. 16; RR 1.07, 95% CI 0.54,2.12; p=0. 84), hospitalization (33 vs. 50; RR 0.67, 95% CI 0.32,1.40; p=0.28), multi-drug resistant gram-negative bacilli bacteriuria (from scheduled and suspected UTI urine cultures) (9 vs. 24; RR 0.38, 95% CI 0.10,1.46; p=0.16), antibiotics administered for suspected UTI (692 vs. 909; RR 0.77, 95% CI 0.44,1.33; p=0.34), or total antimicrobial utilization (1415 vs. 1883; OR 0.76, 95% CI 0.46,1.25; p=0.28)
- **Author's conclusion:** Among older women residing in nursing homes, administration of cranberry capsules, compared with placebo, resulted in no significant difference in presence of bacteriuria plus pyuria over 1 year

STRENGTHS

- Using prior studies to make sure the dose that was used in this study was appropriate
- Using double-blind, placebo controlled design
- Using randomization to create the study and control group
- Inclusion and exclusion criteria helped to maximize the number patients completing the study
- The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The cranberry and placebo capsule manufacturer had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication
- Long study duration
- The study measured and reported adherence levels and adherence was high (study drug adherence was 80.1%)

LIMITATIONS

- Extensive exclusion and inclusion criteria, limiting its ability to be applied to the general population
- Because of the nature of the study population and the methods the study used to measure outcomes, there was a large number of patients that did not complete the study
- The study did not control for all of the possible confounding variables including things like hydration which could have made an impact on the results
- The study patient population had some differences at baseline in comorbid conditions, UTI rates, and antibiotic use rates
- The baseline rate of bacteriuria plus pyuria and percentage of *E.coli* bacteriuria in this trial population was lower than in the pilot dosing study
- This study enrolled women with or without bacteriuria plus pyuria at baseline. Therefore, it was not possible to definitively determine the specific role of cranberry capsules for prevention of new occurrence of bacteriuria plus pyuria among women without bacteriuria plus pyuria at baseline, nor for reduction of bacteriuria plus pyuria among women with prevalent bacteriuria plus pyuria at baseline

CONCLUSION

- Although this study shows that patients that reside in nursing homes and are 65 years of age and older may not experience any statistically significant benefits to taking cranberry capsules when analyzing the presence of bacteriuria plus pyuria, symptomatic UTI, all-cause death, all-cause hospitalization, all multi-drug antibiotic resistant organisms, antibiotics for suspected UTI, and total antimicrobial prescriptions, future research is needed because of the numerous things that may have influenced the results of the study.
- Future research: First, a study should be done with a higher sample size to account for the high level of dropouts seen in this population. In addition, a different method of urine collection should be used in order to determine if patients who have a catheter or other issues incompatible with the way this study was conducted would have any influence over the results of the study. Future researchers may also want to study specifically patients with bacteriuria plus pyuria at baseline or without it. Researchers may also want to conduct a similar study that controls for hydration considering this was one of the main differences compared to other studies that did find significant differences with cranberry.

Reference: Juthani-Mehta M, Van Ness PH, Bianco L, et al. Effect of Cranberry Capsules on Bacteriuria Plus Pyuria among Older Women in Nursing Homes: A Randomized Clinical Trial. *JAMA*. 2016; 316(18):1879-1887. doi:10.1001/jama.2016.16141.

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02/28/17