

Cranberries vs Antibiotics to Prevent Urinary Tract Infections: A Randomized Double-blind Noninferiority Trial in Premenopausal Women

BACKGROUND:

- Urinary tract infections occur frequently in women, especially younger women. 20% to 30% of women that have had a UTI will have a recurrent UTI at some point in their life.
- Prophylaxis with antibiotics is often recommended for women who have recurrent UTI, but this can lead to antibiotic resistance. Due to resistance, other non-antibiotic therapies are being explored for the prophylactic treatment of recurrent UTIs.
- Cranberries are believed to be useful as a prophylactic therapy for recurrent UTIs because they can inhibit the attachment of pathogens, specifically *E coli*, to the uroepithelial cell receptors in the urinary tract.

OBJECTIVE:

- To compare 12 months of prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) 480mg daily to cranberry capsules 500mg twice daily for the prevention of recurrent UTIs in premenopausal women.

METHODS:

- **Design:** Controlled experiment – randomized, double-blind, double-dummy, noninferiority trial
- **Duration:** Recruited from January 1, 2005 through August 31, 2007 and treated with 12 months of prophylaxis with an additional follow up 3 months after prophylaxis.
- **Inclusion criteria:** Premenopausal women, 18 years of age or older, history of at least 3 symptomatic UTIs in the previous year
- **Exclusion criteria:** Symptoms of a UTI at inclusion, use of antibiotics or cranberries in the previous 2 weeks, relevant interactions with existing medication or contraindications for TMP-SMX (known allergy) or cranberries (oral anticoagulants or renal stones), pregnancy (or desire for pregnancy), breastfeeding, or a history of renal transplantation
- **Patients enrolled:** 221 premenopausal women with recurrent UTIs were recruited, 110 women were randomized to the TMP-SMX group and 111 women were randomized to the cranberry group.
- **Drug regimens:** Women were randomized to 12 month's prophylactic treatment with either:
 - TMP-SMX 1 tablet 480mg at night and 1 placebo capsule twice daily
 - Cranberry extract 1 capsule 500mg twice daily and 1 placebo tablet at night
 - The women were to collect their urine and feces monthly for analysis of antibiotic resistance of *E coli* isolates
- **Primary outcome measure:** Mean number of symptomatic UTIs, referred to as clinical recurrences (CR), over the 12 month period, the proportion of patients with at least 1 symptomatic UTI during 12 month prophylaxis use, the median time to the first symptomatic UTI, and the percentage of *E coli* isolates from feces and urine of asymptomatic women that was resistant to TMP-SMX at 1 and 12 months.
- **Secondary outcome measures:** Mean number of microbiologically confirmed symptomatic UTIs, referred to as microbiologic recurrences (MR), the percentage of patients with at least 1 MR, the median time to first MR during the 12 months of prophylaxis use and in the 3 months after prophylaxis use, the prevalence of asymptomatic bacteriuria at 1 and 12 months of prophylaxis use, and proportion of patients experiencing serious adverse effects.
- **Power:** For 80% power, the sample size in each group needed to be 118. The sample size was not large enough to have 80% power.
- **Data handling:** Intentions to treat

RESULTS:

- **Completion of study:**
 - 54 women in the TMP-SMX group appeared at their 15 month follow-up
 - 45 women in the cranberry group appeared at their 15 month follow-up
- **Primary outcome measure:**
 - At 12-month prophylaxis, the mean number of clinical recurrences was 1.8 (CI=0.8-2.7) in the TMP-SMX group and 4.0 (CI=2.3-5.6) in the cranberry group (p=0.02).

- Proportion of women with at least 1 symptomatic UTI was higher in the cranberry group in comparison to the TMP-SMX group (78.2% vs 71.1%, respectively; p=0.03)
- Median time to first clinical recurrence was 8 months for TMP-SMX group and 4 months for cranberry group (p=0.03).
- 3 months after prophylaxis, the mean number of CRs was 0.5 (CI=0.3-0.7) in the TMP-SMX group and 0.7 (CI=0.4-0.9) in the cranberry group (p=0.30).
- After 12 month prophylaxis with TMP-SMX, there was an increase in resistance to TMP-SMX, amoxicillin, and the quinolones
- **Secondary outcome measure:**
 - At 12 month prophylaxis, the mean number of microbiologic recurrences was 0.8 (CI=0.4-1.1) in the TMP-SMX group and 1.2 (CI=0.8-1.5) in the cranberry group (p=0.15).
 - *E coli* was most commonly the cause of the UTI in both groups, 78.9% in the TMP-SMX group and 75.9% in the cranberry group.
 - After 1 month of prophylaxis treatment, 26.5% of women in the TMP-SMX group and 36.0% of women in the cranberry group had asymptomatic bacteriuria.
 - After 12 months of prophylaxis treatment, 30.2% of women in the TMP-SMX group and 37.0% of women in the cranberry group has asymptomatic bacteriuria.
 - No statistically significant differences between the adverse events or serious adverse event from TMP-SMX in comparison to the cranberries.
- **Author's conclusion:**For the prophylactic treatment of recurrent UTIs in premenopausal women, TMP-SMX 480mg daily is more effective than cranberry capsules 500mg twice daily. However, TMP-SMX is associated with a greater risk of developing antibiotic resistance.

STRENGTHS:

- The study had a long intervention period of 12 months with a 3 month follow up after discontinuation of the study treatment.
- It was a controlled study, which is the gold standard. Also, it was a double-blinded and double-dummy study design, which decreases the risk of bias.

LIMITATIONS:

- Appropriate power was not met due to an inadequate, decreased sample size
- Clinical recurrence was not diagnosed from a microbiologic standpoint (no cultures), only based on the women's' symptoms
- Compliance with cranberry prophylaxis was not measured
- Compliance with TMP-SMX was only measured by the presence of antibacterial activity, it is not known if the women took the antibiotic every day or if they took them correctly

CONCLUSIONS:

- Recurrent UTIs are a common problem in premenopausal women. Prophylactic treatment with the antibiotic TMP-SMX 480mg daily for recurrent UTIs can decrease the number of UTIs in 1 year, but is associated with building resistance. The risks and benefits need to be weighed for taking long-term antibiotics, especially with the increased risk for resistance.
- Cranberry capsules may be helpful in preventing recurrent UTIs, but based on the results from this study, are not the best prophylactic therapy for recurrent UTIs in premenopausal women.
- Due to limitations associated with this study, further research should be performed comparing cranberry therapy with prophylactic antibiotics for recurrent UTIs.

Reference:

Beerepoot MAJ, terRiet G, Nys S, van der Wal WM, de Borgie CAJM, de Reijke TM, et al. Cranberries vs antibiotics to prevent urinary tract infections: A randomized double-blind noninferiority trial in premenopausal women. Arch Intern Med. 2011 Jul;171(14):1270-1278.