A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women

Lynn Stothers, MD

Department of Surgery, Division of Urology, and Department of Health Care and Epidemiology, University of British Columbia, Vancouver, B.C., Canada

STOTHERS L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. The Canadian Journal of Urology. 2002;9(3):1558-1562.

Purpose: To determine, from a societal perspective, the effectiveness and cost effectiveness of concentrated cranberry tablets, versus cranberry juice, versus placebo used as prophylaxis against lower urinary tract infection (UTI) in adult women.

Materials and methods: *One hundred fifty sexually active women aged 21 through 72 years were randomized for one year to one of three groups of prophylaxis: placebo juice + placebo tablets versus placebo juice + cranberry tablets, versus cranberry juice + placebo tablets. Tablets were taken twice daily, juice 250 ml three times daily. Outcome measures were: (1) a >50% decrease in symptomatic UTI's per year (symptoms + ≥ 100 000 single organisms/ml) and (2) a >50% decrease in annual antibiotic consumption. Cost effectiveness was calculated as dollar cost per urinary tract infection prevented. Stochastic tree decision analytic modeling was used to identify specific clinical scenarios for cost savings.*

Results: *Both cranberry juice and cranberry tablets statistically significantly decreased the number of patients experiencing at least 1 symptomatic UTI/year (to 20% and 18% respectively) compared with placebo (to 32%) ($p<0.05$). The mean annual cost of prophylaxis was $624 and $1400 for cranberry tablets and juice respectively. Cost savings were greatest when patients experienced >2 symptomatic UTI's per year (assuming 3 days antibiotic coverage) and had >2 days of missed work or required protective undergarments for urgency incontinence. Total antibiotic consumption was less annually in both treatment groups compared with placebo. Cost effectiveness ratios demonstrated cranberry tablets were twice as cost effective as organic juice for prevention.*

Conclusions: *Cranberry tablets provided the most cost-effective prevention for UTI.*

Key Words: urinary tract infection, cost effectiveness

Introduction

Cranberries (*Vaccinium macrocapon*) and cranberry juice were used for centuries by Native Americans as a food source and for medicinal purposes including treatment of bladder and kidney disease. Once introduced to Europe, they were used in the treatment of stomach ailments, blood disorders, liver problems, fevers and scurvy. In the late 1800's and early 1900's, cranberries were used as a treatment for bladder gravel and 'blood toxins'. Cranberries are commonly believed to be effective in preventing or treating urinary tract infections, and are one of the five most-

Accepted for publication April 2002

Address correspondence to Dr. Lynn Stothers, #590 – 1144 Burrard Street, Vancouver, BC V6Z 2A5 Canada

commonly-used herbal remedies.[1] However, the evidence supporting the use of cranberries in the prevention of UTI has not been strong.[2]

We conducted a study to evaluate the effectiveness and cost effectiveness of cranberry juice and cranberry extract tablets in the prevention of UTIs. We hypothesized that patients receiving tablets of cranberry extract would experience a mean of at least 50% fewer UTIs, defined as symptomatic, culture-positive infection with ≥100 000 single organisms per ml, compared with those in the placebo group. To test the hypothesis, we chose a pure, unsweetened organically-grown cranberry juice, and a tablet containing cranberry extracts and cranberry juice concentrate.

Materials and methods

This study was a randomized double-blind controlled trial that was peer reviewed and approved by the institutional ethics review board. All patients had a complete history, physical examination, urinalysis and urine culture prior to enrolment in the study. Subjects invited to participate in the study had had at least two symptomatic, single-organism, culture-positive urinary tract infections in the prior calendar year, but were currently free of urinary tract infection on urinalysis and culture. Exclusion criteria were neurogenic bladder dysfunction, pregnancy, allergy to cranberry products, insulin-dependent diabetes, immunosuppresive disease, steroid use, or intermittent or indwelling catheterisation. Patients signed an informed consent that described the need for dietary restriction of additional cranberry products during the study and the fact that they might be randomized to the group that received a placebo treatment. Patients who provided informed consent were randomized in blocks of 10 to one of the 3 arms of the study:

1) Placebo arm: a placebo tablet twice daily and 250 ml of placebo juice (filtered water with food coloring plus 20 ml pineapple juice) three times per day,
2) Tablet arm: one tablet of concentrated cranberry juice (at least 1:30 parts concentrated juice) twice daily and 250 ml of placebo juice three times per day, and
3) Juice arm: 250 ml of pure unsweetened cranberry juice three times per day and one tablet of placebo twice daily. The volume of juice was selected to make the juice intake comparable to what was available in tablet formulations.

The pharmacy dispensed the prepared juices (placebo or cranberry juice) and tablet packages (placebo or cranberry extract tablets). The investigator was unaware of the arm to which patients were assigned.

Patients remained on the protocol for 12 months. Symptoms of lower urinary tract infection were treated with a culture-directed prescription of antibiotics for 3 days and then prophylaxis was restarted. Compliance was monitored by a pill count and questioning regarding fluid intake. Side effects were monitored by questioning at routine visits every 8 weeks. A positive culture was defined as > or equal to 100 000 single organisms per millilitre.

Cost effectiveness was defined as dollar cost per UTI prevented. Patients' receipts, interviews and medical records provided data on patient costs. Direct patient costs included costs of cranberry juice or tablets or bottled water, antibiotics including dispensing fees, and costs of complications such as time lost from work and taxi/parking receipts for doctors appointments. Indirect patient costs included lost wages. Time lost from work was valued at the group mean pre-study gross weekly income, which was $675 per week. Direct health sector costs included physician visits and investigations. Stochastic tree decision models were used to identify cost saving scenarios.

Statistical methods included ANOVA for statistical significance of the mean number of infections in each arm of the trial. Power was set at 80% and significance was defined as a $p <$ or equal to 0.05.

Results

One hundred fifty sexually active women aged 21-72 years (mean 42 years) participated, with 50 randomized in blocks of 10 to each study arm. Fifty-two women were menopausal and 15 were non-insulin-dependent diabetics. One hundred seventeen worked outside of the home with a mean pre tax gross income of $35 000 per year (range $15 000 to $62 000). The mean number of UTI's prior to the study was 2.8 (range 2 to 5) in the prior calendar year. Table 1 presents these data by group.

Compliance rates by each of the groups by month are shown in Figure 1.

The number experiencing at least one urinary tract infection during treatment was 16 (32%) in the placebo group, 10 (20%, $p<0.05$) in the juice group and 9 (18%, $p<0.05$) in the tablet group. The mean number of UTIs in a calendar year following treatment was 0.72 in the placebo group, 0.30 in the juice group ($p<0.05$) and 0.39 in the tablet group ($p<0.05$).

Complications reported by patients in the placebo

TABLE 1. **Comparison of characteristics (no significant differences between groups, >0.05)**

	Placebo (N=50)	Tablet (N=50)	Juice (N=50)
Age (range and (mean))	21-72 (43)	23-68 (40)	21-70 (44)
Pre-Post menopause	34:16	30:20	37:13
Income ($mean annual)	40 000	34 500	37 800
UIT's in preceding year (range (mean))	2-5 (3.5)	2-4 (3.1)	2-5 (3.3)

group were: headache (2 patients) and mild nausea (2 patients). None of these patients discontinued treatment. In the juice group symptoms of reflux were reported by 3 patients, 2 of whom dropped out of the study due to this problem. Complications reported in the tablet group were: mild nausea (4 patients) and increased frequency of bowel movements (1 patient). None of these complaints required discontinuation of treatment. Eight patients complained about the size of the tablets and two stated they were difficult to swallow.

The annual cost of prophylaxis was $624 with cranberry tablets (calculated as CDN$0.73 per capsule, 1 capsule twice daily, and 14% tax) and $1400 with cranberry juice (calculated as CDN$5.30 per litre, 250 ml taken three times per day, and no tax). Cost effectiveness ratio for juice was CDN$3333 per UTI prevented with 82% direct patient costs, 6% indirect patient costs and 11% direct health sector costs. The cost effectiveness ratio for tablets was CDN$1890 per UTI prevented with 73% direct patient costs, 5% indirect patient costs and 21% direct health sector costs.

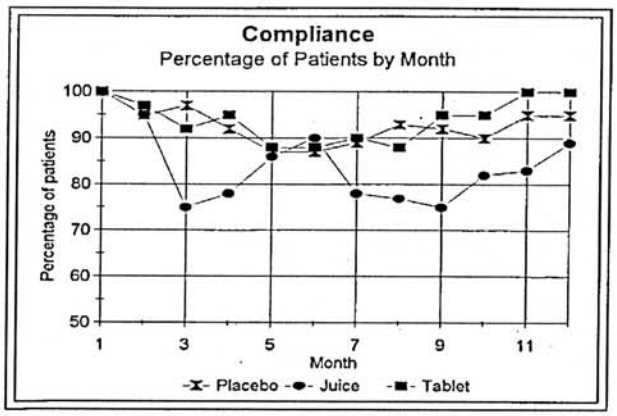

Figure 1. Compliance with treatment regimens, showing that those in the cranberry juice group were less compliant that those in the placebo and tablet groups, with compliance dropping below 80% during 5 of 12 months.

Before the study, the mean number of days of antibiotic use in a calendar year by the 150 women was 6 (range 3 to 17). This decreased to a mean of 4.0 in the placebo group (range 0-9), 2.9 in the juice group and 2.1 in the tablet group. The mean annual cost of antibiotics used per patient was $18.60 (range $7.50 - $90.00) prior to the study. During the study this was a mean of $7.30 (range $0 - $51.10) in the placebo group, $5.13 (range $0 - $42.00) in the juice group and $4.70 (range $0 - $42.25) in the tablet group.

Discussion

This study found that cranberries are an effective means of preventing urinary tract infections in women who experience recurrent UTIs. We found that 40% fewer women experienced UTIs when receiving cranberry products compared with placebo juice (19% versus 32%), and that on average, they experienced half the number of UTIs per year. There was also a decrease in UTIs in the placebo group compared with the previous year, which may be related to the increased volume of liquid consumed in the placebo juice.

A Cochrane systematic review of the literature in 2000[1] found six trials examining the effectiveness of cranberries for prevention of UTIs. Of the six, two were excluded because they did not have UTI as an outcome measure. None of the remaining four met the criteria for adequate randomization. Of the four studies, three were cross-over studies.[3-5] In two of these, the sample size was extremely small. In Foda's study, only 21 completed study,[4] and in Haverkorn's study, only seven subjects were included in the final analysis.[5] The fourth study was a parallel groups study,[6] but only 10 patients completed this study. Only two of the trials were double blind. The strongest study[3] demonstrated in a randomized double-blind study that drinking 300 ml of cranberry cocktail daily

reduced the incidence of urinary tract infections in elderly women by almost 50%. However, there were significant baseline differences between the two groups in this study. Although two of the other three studies also found that cranberries were effective, the conclusion of the review was that, because the study designs were so poor, there was no conclusive evidence that cranberries are effective in preventing UTIs. The recommendation was that there was a need for randomized controlled, blinded studies.

Since the Cochrane review, there have been several additional reports of studies of cranberry juice in the prevention of UTI. Schlager et al reported no effect on the incidence of bacteriuria in children with neurogenic bladders.[7] The quantity of juice was 2 ounces of concentrate or placebo, independent of age or size. The report provides no information on the level of compliance, which may have been quite low, particularly in the younger children. Reid et al reported an open cross-over pilot study in 15 spinal cord injured patients.[8] That study suggested that cranberry juice consumption decreased both Gram negative and Gram positive bacterial adhesion. Kontiokari et al reported a randomized open study comparing three arms (cranberry-lingonberry juice, lactobacillus-containing drink, and no intervention) conducted in Finland.[9] That study found that cranberry-lingonberry concentrate was effective in reducing the incidence of recurrent urinary tract infections compared with no intervention, but a drink containing lactobacilli was not.

The mechanism of therapeutic action of cranberries remains unclear. In 1923, researchers demonstrated that consumption of cranberries resulted in acidification of the urine, and made the theoretical leap that it was the hippuric acid that provided the curative effect,[10] but this was refuted in 1959.[11] In 1984, Sobota reported that cranberry juice interfered with the attachment of bacteria to uroepithelial cells, and thus had potential in the treatment of UTI.[12,13] Recent work supports the theory that it is interference with bacterial attachment that provides therapeutic effect. Interference with attachment has been documented with *E coli, Proteus, Klebsiella, Enterobacter,* and *Pseudomonas.* Several molecules have been proposed as the source of the interference: hippuric acid,[14] fructose,[15] ascorbic acid,[16] and proanthocyanidins.[17,18] *Vaccinium* species, cranberries and blueberries, are unique in their high concentrations of quinic acid, which is aromatized to benzoic acid, and with the addition of glycine, is changed to hippuric acid. Hippuric acid is found in the urine following consumption of cranberries, and has been shown to interfere with bacterial attachment.[3] Fructose, found in all fruit, prevents adhesion of type 1-fimbriated bacteria.[15] More recently, proanthrocyanidins found in cranberries have been shown to prevent attachment of P-fimbriated *E coli* to cellular surfaces.[15,18]

Whatever the mechanism of therapeutic action, the evidence that ingestion of cranberry products prevents urinary tract infections is mounting. It is now necessary to determine the most cost-effective delivery method. The cost of preventing a single UTI in this study was quite high. However both the quality and quantity of juice, and thus the cost, were very high. Further research is needed to determine the amount of cranberry juice or strength/size of tablets required to be effective. It may be possible to reduce the amount of juice significantly, or to use cranberry cocktail. Cranberry juice as a pure unsweetened juice is quite unpalatable, and has even been reported to be "undrinkable". Patients are more likely to regularly consume cranberry juice cocktail preparations, which use dilute juice and which are sweetened with fructose (which has also been shown to have therapeutic effect on UTIs), or a tablet containing the necessary active agents. If cranberry juice cocktail can be shown in a blinded, placebo-controlled study to be effective, this may well be the treatment of choice as it is readily available and costs much less than the organic, pure, unsweetened juice used in this study. Alternatively, blueberries or blueberry juice, which are much more palatable, may also be effective.[19]

Complications reported with use of cranberry as an herbal medication are rare. There has only been one report of an adverse effect (an allergic reaction) made to the US Food and Drug Administration, Special Nutritionals Adverse Event Monitoring System, a voluntary reporting system *(http://vm.cfsan.fda.gov/cgi-bin/aems2.cgi?REPNO=12864).*

This study had several limitations:

- The placebo juice was not an exact match for the pure unsweetened cranberry juice, but a good visual match was made, and the participants were not able to compare the two, as there was no cross-over phase.
- Cranberry products are not regulated, and therefore the concentration of active ingredients was not known. Therefore, it was not possible to compare the strength of the products, and the concentrations may have fluctuated between batches of the same product.
- Compliance was measured by self-report, which may be inaccurate.
- The study only enrolled non-pregnant women, and therefore the applicability of the results to children, males, or pregnant women may be questioned.

Women who experience recurrent UTIs are often prescribed low-level prophylactic antibiotic regimens, but increasingly, there are reports of antibiotic-resistant strains.[20] Thus, an agent such as cranberry juice that is not specific to a particular bacterial strain is desirable if it is effective.

Conclusions

Cranberry juice and cranberry tablets with increased fluid intake are more effective than fluid intake alone in preventing urinary tract infections in sexually active women with recurrent UTIs. Our results support the findings of other randomized studies involving adult women,[9] that cranberry products should be offered as an option in the clinical management of recurrent UTI's. Ten to fifteen percent of women will experience fewer clinical lower urinary tract infections if cranberry products are added to the conservative measure of simply increasing fluid intake.

Further studies are required to determine the optimum amount, and the most cost-effective method of delivery. □

References

1. Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections (Review). Cochrane Database Syst Rev 2000; 2:CD001321.
2. Stamm WE, McKevitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. *Rev Infect Dis* 1991;13(5):1024-1025.
3. Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994;272(8):588-589.
4. Foda MM, Middlebrook PF, Gatfield CT, Potvin G, Wells G, Schillinger JF. Efficacy of cranberry in prevention of urinary tract infection in a susceptible pediatric population. *Can J Urol* 1995;2(1):98-102.
5. Haverkorn MJ, MandigersJ. Reduction of bacteriuria and pyuria using cranberry juice [letter]. *J Am Med Assoc* 1994;272(8):590.
6. Walker EB, Barney DP, Mickelsen JN, Walton RJ, Mickelsen RA. Cranberry concentrate: UTI prophylaxis (letter). *J Fam Pract* 1997;45(2):167-168.
7. Schlager TA, Anderson S, Trudell J, Hendley JO. Effect of cranberry juice on bacteriuria in children with neurogenic bladder receiving intermittent catheterization. *J Pediatr* 1999;135(6):698-702.
8. Reid G, Hsiehl J, Potter P, Mighton J, Lam D, Warren D, Stephenson J. Cranberry juice consumption may reduce biofilms on uroepithelial cells: pilot study in spinal cord injured patients. *Spinal Cord* 2001;39(1):26-30.
9. Kontiokari T, Sundqvist K, Nuutinen M, Pokka T, Koskela M, Uhari M. Randomised trial of cranberry-lingonberry juice and *Lactobacillus* GG drink for the prevention of urinary tract infections in women. *Br Med J* 2001;30;322(7302):1571.
10. Blatherwick NR, Long ML. Studies on urinary acidity. The increased acidity produced by eating prunes and cranberries. *J Biol Chem* 1923;57:815-818.
11. Bodel PT, Cotran R, Kass EH. Cranberry juice and the antibacterial action of hippuric acid. *J Lab Clin Med* 1959;54:881-888.
12. Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *J Urol* 1984;131(5):1013-1016.
13. Schmidt DR, SobotaAE. An examination of the anti-adherence activity of cranberry juice on urinary and nonurinary bacterial isolates. *Microbios* 1988;55:173-182.
14. Kinney AB, Blount M. Effect of cranberry juice on urinary pH. *Nurs Res* 1979;28(5):287-290.
15. Foo LY, Yu Y, Howell AB, Vorsa N. A-type proanthocyanidin trimers from cranberrry that inhibit adherence of uropathogenic P-fimbriated *Escherichia coli*. *J Nat Prod* 2000;63:1225-1228.
16. Habash MB, Van der Mei HC, Busscher HJ, Reid G. The effect of water, ascorbic acid, and cranberry derived supplementation on human urine and uropathogen adhesion to silicone rubber. *Can J Microbiol* 1999;45(8):691-694.
17. Zafriri D, Ofek I, Adar R, Pocino M, Sharon N. Inhibitory activity of cranberry juice on adherence of type I and type P fimbriated *Escherichia coli* to eucaryotic cells. *Antimicrob Agents Chemotherapy* 1989;33(1):92-98.
18. Howell AB, Vorsa N, Marderosian AD, Foo LY. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial surfaces by proanthocyanidin extracts from cranberries. *N Engl J Med* 1998;339:1085-1086.
19. Ofek I, Goldhar J, Sharon N. Anti-*escherichia coli* adhesin activity of cranberry and blueberry juices. *Adv Exp Med Biol* 1996;408:179-183.
20. Bennett J, Brown CM. Use of herbal remedies by patients in a health maintenance organization. *J Am Pharm Assoc* (Wash) 2000;40(3):349-351.