Cranberry Juice for the Prevention of Pediatric Urinary Tract Infection: A Randomized Controlled Trial

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Abbreviations and Acronyms

PAC = proanthocyanidin

UTI = urinary tract infection

VUR = vesicoureteral reflux

Study received research ethics board approval.

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Purpose: Proanthocyanidins found in cranberry have been reported to have in vitro and in vivo antibacterial activity. We determined the effectiveness of cranberry juice for the prevention of urinary tract infections in children.

Materials and Methods: A total of 40 children were randomized to receive daily cranberry juice with high concentrations of proanthocyanidin vs cranberry juice with no proanthocyanidin for a 1-year period. The study was powered to detect a 30% decrease in the rate of symptomatic urinary tract infection with type I and II errors of 0.05 and 0.2, respectively. Toilet trained children up to age 18 years were eligible if they had at least 2 culture documented nonfebrile urinary tract infections in the calendar year before enrollment. Patients with anatomical abnormalities (except for primary vesicoureteral reflux) were excluded from study. Subjects were followed for 12 months. The participants, clinicians, outcome assessor and statistician were all blinded to treatment allocation.

Results: Of the children 39 girls and 1 boy were recruited. Mean and median patient age was 9.5 and 7 years, respectively (range 5 to 18). There were 20 patients with comparable baseline characteristics randomized to each group. After 12 months of followup the average incidence of urinary tract infection in the treatment group was 0.4 per patient per year and 1.15 in the placebo group ($p = 0.045$), representing a 65% reduction in the risk of urinary tract infection.

Conclusions: Cranberry juice with high concentrations of proanthocyanidin appears to be effective in the prevention of pediatric nonfebrile urinary tract infections. Further studies are required to determine the cost-effectiveness of this approach.

Key Words: urinary tract infections, primary prevention, secondary prevention, Vaccinium macrocarpon, randomized controlled trial

Recurrent urinary tract infections are one of the most common reasons for pediatric urology referral. The management goals include identification of any correctible anatomical or functional predisposing aberrations, treatment of the UTI and prevention of recurrence. Probiotics and natural food products have been used in the prevention of UTIs but high quality studies are scarce.

In this randomized placebo controlled study we evaluated the effectiveness of cranberry juice with high concentrations of proanthocyanidins, the substance most likely responsible for the antibacterial activity of cranberry, in the prevention of pediatric UTIs. We hypothesized that the consumption of cranberry juice with high concentrations of PAC would reduce the incidence of UTIs in children compared to juice with no PAC.

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METHODS AND PATIENTS

The study was approved by University of British Columbia Research Ethics Board. We recruited the participants from the pediatric urology clinic at British Columbia Children's Hospital. Inclusion criteria were any toilet trained child 18 years old or younger with at least 2 culture documented symptomatic UTIs in the calendar year before recruitment.

Patients with known anatomical abnormalities (posterior urethral valves, neurogenic bladder, any urinary obstruction) were excluded from study. Primary VUR was not considered an exclusion criterion. Logistically since we were only able to deliver the juice to metropolitan Vancouver, patients from more remote areas of the province were excluded from study.

Urinary infection was defined as a positive culture of a midstream sample with a uropathogenic bacterium at 100 million cfu/l (10^5 per ml) in symptomatic children with or without fever. We accepted lower counts (10 million cfu/l) if the patient had typical symptoms of UTI (dysuria, frequency, hematuria etc) and positive white blood cells and/or nitrites on urinalysis. Asymptomatic bacteriuria was not considered an end point. After explaining the study and obtaining consent, patients were assigned to the placebo or experimental group using a computer generated random number table. The randomization was concealed.

Ocean Spray Cranberries, Inc. provided the research grade juice and placebo. The 2 types of juice were identical in terms of color, taste and packaging. The experimental group received 2 cc/kg cranberry juice containing 37% PAC and the placebo group was given the same volume of juice with no PAC or other cranberry products. The dose was calculated based on a previous adult study as well as the appropriate volume a child can consume.[1] The juice was delivered to the participant's house under light and temperature control on a monthly basis for 1 year. During this time the participants were followed with alternating clinic visits and telephone calls by a nurse clinician every 3 months. With each clinic visit a urine sample was sent for PAC measurement, and if the child was symptomatic, it was sent for urinalysis and culture. The number of bottles of juice used during followup was documented by the research nurse as a measure of compliance.

Sample size calculation was based on type I and II errors of 0.05 and 0.2, respectively. Based on the available literature our primary end point was a 30% reduction in infection rate in 12 months.[2] Power calculation estimated the required sample size to be 40 (20 per arm). To avoid contamination patients were asked to not use any other cranberry products for the duration of the study. The attending urologists, research nurse, outcome assessor and statistician were all blinded to the group allocations.

UTI rates were calculated per patient per year. Rate ratio and corresponding 95% CI were calculated. Statistical significance was considered if the p value was lower than 0.05. The intent to treat principle was followed.

RESULTS

The table shows the baseline characteristics of the patients. The 2 groups were similar in most important baseline factors. Bowel and bladder dysfunction was common in both groups (90%). VUR was known in 4 of 20 in the experimental and 2 of 20 in the placebo group. Of the 4 patients in the experimental group 3 underwent endoscopic treatment of VUR and 1 underwent ureteral reimplantation. Both patients in the placebo group with reflux underwent endoscopic treatment. Before enrollment the average number of infections was 2.4 per year per patient in the experimental group and 2.5 in the placebo group. The infection before recruitment was due to Escherichia coli in 65%, other enteric gram-negative bacilli in 27%, gram-positive cocci in 8% and more than 1 type of bacteria in 5% of the patients.

Patient baseline characteristics

	Experimental Group	Placebo Group
Median age (range)	7 (5–18)	7 (5–17)
No. female (%)	19 (95)	20 (100)
No. bladder + bowel dysfunction (%)	18 (90)	18 (90)
Av UTIs in yr before recruitment	2.4	2.5
No. VUR (%)	4 (20)	2 (10)

There were 6 patients in each group who did not complete the study. Average followup for these patients was 3 months. All patients were included in the analysis. Reasons for dropout included relocation (1), refusal to drink the juice (3), contrary advice from family doctor (1), family perception of juice ineffectiveness (4), skin rash (1) and unknown (2). Five UTIs were identified in 5 patients in the experimental group as opposed to 15 in 8 patients in the placebo group.

Median followup in both groups was 12 months. Including all randomized subjects with any followup yielded rates of 0.02 and 0.06 UTIs per patient per year in the experimental and placebo groups, respectively. When analyzing patients who completed the study the average incidence of UTI in the treatment group was 0.4 per patient per year vs 1.15 in the placebo group ($p = 0.045$). The rate ratio was estimated at 0.33 with 95% CI 0.12–0.91 for both as per protocol and intent to treat analyses. This represents a 65% reduction in the risk of UTI in the treatment group receiving cranberry extract.

DISCUSSION

Pediatric urologists are frequently faced with patients with no discernible anatomical abnormalities who experience recurrent UTIs. Important predisposing factors include bowel and bladder dysfunction and genetic predisposition to UTIs. Prophylactic antibiotics may be used along with other interventions to modify these risk factors. With an increase in bacterial resistance and conflicting evidence re-

garding the effectiveness of prophylactic antibiotics, a nonpharmacological measure for the prevention of UTIs has become more attractive.[3] There are many claims about the beneficial effects of dietary supplements and natural products for the prevention of UTIs. Prime examples include d-mannose, probiotics and cranberry products.

Cranberry or vaccinium macrocarpon has been used since as early as the 1800s for disorders of the bladder. Initial studies focused on the role of hippuric acid as the antibacterial substance in cranberry products. Hippuric acid is derived from quinic acid found in the cranberry. Subsequent studies did not confirm the suggestion that hippuric acid possessed antibacterial properties. To produce significant levels of hippuric acid in the urine one should drink 240 cc cranberry juice at an 80% concentration.[4] Other substances found in cranberry with in vitro and in vivo antibacterial activity are proanthocyanidins. These are flavonoid compounds in dimer and trimer forms. PACs competitively bind to P fimbriae of enteric bacteria, thus preventing adhesion of the microorganisms to the urothelium.[5] P fimbriae are mannose resistant adhesins found on uropathogenic bacteria. Apart from facilitating the initiation of UTIs they may also contribute to inflammatory changes and renal scar formation.[6,7] Type A PAC is found in the cranberry, and has higher anti-adhesion effects than type B, which is found in apples and green tea.[8] The 2 types of juice used in this study had a 37% concentration of PAC or no PAC. Unfortunately, at this time the data regarding PAC concentration in the urine of participants are not available for analysis.

In 2008 Jepson and Craig published a systematic review of randomized controlled trials on cranberry for preventing UTIs.[2] They identified 10 studies. In 7 studies juice was used against placebo and in 2, tablets vs placebo. One study had 3 arms of juice vs tablets vs placebo. Meta-analysis of the results in 665 patients revealed a beneficial effect for the prevention of UTIs (RR 0.66, 95% CI 0.47–0.92). Subgroup analysis did not reveal a significant effect in elderly patients or in those with neurogenic bladder. No data were presented for children. In our study we demonstrated a significant difference in the rate of infection between 2 groups of children, with 1.15 UTIs per person per year in the placebo group vs 0.4 in the experimental group, representing an approximate risk reduction of 65%. None of our patients had a febrile UTI during followup.

In contrast, Beerepoot et al found more urinary infections in patients who received cranberry extract compared to those who had antibiotic prophylaxis (78.2% vs 71.1% of patients with at least 1 UTI in 12 months).[9] This study was done in premenopausal women, and it is difficult to compare the results to those of our study since the population and the interventions were dissimilar.

In a recently published randomized controlled study by Salo et al the effect of cranberry juice was compared to placebo in preventing UTI recurrence in children.[10] This study is different from our trial in several respects. For example, almost 45% of participants in the study by Salo et al were toddlers and only 30% had more than 2 UTIs at baseline. Patients with moderate/high grade reflux were excluded from analysis. The prevalence of bowel and bladder dysfunction was not clear. Interestingly the authors did not demonstrate a significant difference in the proportion of children who had at least 1 UTI after entering the study, but when the incidence density (UTIs per person per year) was compared the treatment group showed a 45% lower incidence density (0.25 vs 0.46), which was similar to our results.

Another randomized trial in female, sexually active college students did not show a significant reduction in the recurrence of UTIs when cranberry juice was compared to placebo.[11] This study also differs from our trial in several aspects. The study populations were considerably different, and it is well-known that the pathophysiology of UTIs is dissimilar between sexually active adult women and children.[12] In addition, the authors followed the subjects for a maximum of 6 months and did not assess rate ratios.[11]

In their systematic review Jepson and Craig identified several major methodological issues with previous trials, mainly a lack of standardization of dose and high dropout rates, especially when juice was used.[2] In our study the dose and concentration of the active ingredient were standardized. PACs are light and temperature sensitive. Therefore, we followed strict light and temperature protection guidelines, keeping juice bottles in a refrigerator in cardboard boxes at all times.

We also experienced a high dropout rate. After an average of 3 months 6 patients in the placebo group and 6 in the treatment group dropped out of study. Since the dropout was equal in both groups, we do not believe this has biased the results. We also used intent to treat analysis, which includes patients who dropped out.

Bowel and bladder dysfunction is a well-known predisposing factor in patients with recurrent UTIs,[13] and is clearly seen in our series. Approximately 90% of our patients had bowel and bladder dysfunction distributed similarly in the 2 arms of the study. Diagnosis of this condition was made by a pediatric urologist based on clinical grounds. All these children had counseling sessions with a nurse clinician to achieve better bladder habits. Constipation was aggressively treated with laxatives and dietary changes.

The ancillary treatments were identical in the 2 groups.

The small sample size in this study is a reflection of the fact that we set the clinically significant difference at 30%, which is a relatively large risk reduction. We would like to emphasize that the findings of this study should not be construed as an endorsement of any commercially available cranberry products. The amounts and concentrations of PAC are not known in most of these products since the products are not regulated. In addition, PACs are degradable molecules. Therefore, the manufacturing date and storage practices are important factors in determining the bioavailability of PAC.

CONCLUSIONS

Cranberry juice with a high concentration of PAC reduces the risk of recurrent UTIs in children with no urological abnormalities. Although this may be an alternative or additional approach in the management of recurrent UTIs, its cost-effectiveness should be studied further before being widely endorsed for the routine management of this problem.

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EDITORIAL COMMENT

This well designed and executed randomized clinical research trial joins other randomized clinical trials that have demonstrated the beneficial effects of cranberry juice in the prevention of clinically significant urinary tract infections in children (reference 10 in article).[1] The findings of this study are notable for several reasons. Plant based products such as cranberries are notoriously unpredictable in their effects because they are an amalgam of chemicals varying in concentration and composition. Nevertheless, we now have 3 independent randomized trials that demonstrate a positive effect in kids. In addition, studies demonstrating the positive benefit of cranberry juice in children stand in contrast to the largely negative results of cranberries for the prevention of urinary tract infection in adults (reference 11 in article). The reasons for this remain unexplored.

As the pediatric community moves away from the routine use of antibiotic prophylaxis for VUR and recurrent urinary tract infections, cranberry prophylaxis is emerging as a viable alternative. It makes one wonder about a new advertising campaign: "Cranberries—they're not just for Thanksgiving anymore!"

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