Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial

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Background. Cranberry juice prevents recurrences of urinary tract infections (UTIs) in adult women. The objective of this study was to evaluate whether cranberry juice is effective in preventing UTI recurrences in children.

Methods. A double-blind randomized placebo-controlled trial was performed in 7 hospitals in Finland. A total of 263 children treated for UTI were randomized to receive either cranberry juice (n = 129) or placebo (n = 134) for 6 months. Eight children were omitted because of protocol violations, leaving 255 children for the final analyses. The children were monitored for 1 year, and their recurrent UTIs were recorded.

Results. Twenty children (16%) in the cranberry group and 28 (22%) in the placebo group had at least 1 recurrent UTI (difference, −6%; 95% confidence interval [CI], −16 to 4%; P = .21). There were no differences in timing between these first recurrences (P = .32). Episodes of UTI totaled 27 and 47 in the cranberry and placebo groups, respectively, and the UTI incidence density per person-year at risk was 0.16 episodes lower in the cranberry group (95% CI, −.31 to .01; P = .035). The children in the cranberry group had significantly fewer days on antimicrobials (−6 days per patient-year; 95% CI, −7 to −5; P < .001).

Conclusions. The intervention did not significantly reduce the number of children who experienced a recurrence of UTI, but it was effective in reducing the actual number of recurrences and related antimicrobial use.

Urinary tract infection (UTI) is one of the most common bacterial infections in childhood [1–4]. About 19%–30% of patients experience a recurrence within 12 months of the initial UTI episode [5–8]. Childhood UTIs cause substantial morbidity and are thought to increase the risk of chronic kidney disease and hypertension, so that children with recurrent UTIs are usually subjected to long-lasting antimicrobial prophylaxis, especially if vesicoureteral reflux (VUR) is present. Adverse reactions and cessation of therapy are common during this long-term antibiotic use, however, and there is an increasing problem of bacterial resistance [8]. Dietary factors are associated with susceptibility to UTIs [9]. Cranberry products appear to be able to prevent UTI recurrences in adult women, but evidence for their efficacy in children is lacking [10–16]. The aim here was to evaluate whether cranberry juice could prevent UTI recurrences in children.

PARTICIPANTS AND METHODS

Population
A group of 263 children aged 1–16 years who had been referred to the pediatric departments of 4 university hospitals in Finland (Oulu, Tampere, Kuopio, and Helsinki) or 3 central hospitals (Joensuu, Lahti, and Kemi) on account of verified UTI in the previous 2 months were recruited for the study over the period
2001–2008. UTI was defined on entry as fever and/or local urinary tract symptoms (dysuria, abdominal/back pain, strong-smelling urine, enuresis) and growth of a single bacterial strain of $\geq 10^5$ colony-forming units (CFUs) per milliliter in a midstream urine sample or a sample taken with a urine bag or catheter, or any growth in a suprapubic bladder aspirate sample, according to the practices of the centers participating in the trial. The same criteria for UTI were used during the trial except that 2 consecutive midstream or bag samples with the same bacterial growth were required. The UTI symptoms were defined in the information sheet and a study diary was given to the parents; the parents were asked to show the diary to the physicians treating the patient. An interval of 10 days or more was required for 2 consecutive UTIs to be recorded as separate events. Urinary tract imaging was performed after the first UTI, as recommended in Finland, that is, urogenital ultrasonography and voiding cystography on all children <2 years of age and ultrasonography only on older children initially, followed by voiding cystography if ultrasonography was abnormal. Children requiring antimicrobial prophylaxis for grade III–V

**Figure 1.** Design of the trial. Patients who dropped out of both groups contributed days at risk until they dropped out.
VUR or other severe genitourethral malformations or for other reasons were excluded (Figure 1). A midstream or bag urine control sample was taken at the beginning and end of the study. Significant bacteriuria was defined as growth of a single bacterial strain of $\geq 10^5$ CFU/mL in a midstream urine sample, or a sample taken with a urine bag.

Study Design
On receipt of written informed consent from the parents, the children were randomized with a block size of 4 by an external statistician to receive 5 mL/kg, up to 300 mL per day of either cranberry juice or placebo juice in 1 or 2 daily doses for 6 months. Each center received sealed envelopes for randomization purposes before the beginning of the recruitment phase, so that the clinicians were unaware of the allocation of individual patients. The parents completed a questionnaire providing background data, nutritional status, and a medical history, and were requested not to give the children any other Vaccinium (eg, cranberry, blueberry, lingonberry) products during the trial. The children were followed up for 1 year, during which consumption of the juice and daily symptoms compatible with UTI were recorded in a diary kept by the parents. The 1-year follow-up period was chosen on the basis of our earlier experience in a trial among adult women [11]. The parents were advised to take the child to their own family physician whenever a fever or local symptoms suggestive of UTI occurred. When UTI was diagnosed, it was treated with a standard antimicrobial therapy regimen, while the child continued taking the juice. If the child had $\geq 3$ UTI recurrences during the trial, antimicrobial prophylaxis for 6 months was recommended. The physicians were asked to record their diagnosis and the resulting treatment on a follow-up sheet, which was returned to the center concerned at the last visit. The results of all urine tests carried out during the follow-up were collected from the laboratory databases. Compliance with the protocol was determined on the basis of the self-report sheets and by counting the empty juice cartridges returned by the parents at the end of the trial.

Cranberry Products and Controls
The commercially available cranberry juice used (Cranberry Classic) containing 41 grams of cranberry concentrate, including flavoring, in 1 L of juice. The placebo drink was almost identical in appearance, smell, taste, and color, but did not contain either fruit or berry extracts. The juices were supplied in similar white, coded cartridges containing 200 mL. The nutritional values of the drinks resembled those of commonly available fruit and berry juices. Both products were manufactured and provided by Ocean Spray Cranberries. The products concerned were shown to be safe and acceptable to children in our previous study [17]. The families either visited or called the nurse or physician responsible every 3 months for inspection of the self-report sheets and replenishment of the juice supplies as required.

Sample Size
We considered a 50% reduction in recurrences to be clinically important, an effect that was regarded as attainable on the basis of our earlier trial [11]. The sample size calculations were based on earlier reports in which up to 30% of children were said to experience a new episode of UTI within 12 months [6, 7]. To detect a reduction in recurrences to 15% with a 2-tailed $\alpha$ of .05 and a power of 80%, and estimating that 10% of subjects will drop out, it was decided that 130 children were needed in each group.

End Points
The primary end point was the occurrence of the first UTI episode during the 12-month follow-up. Secondary end points were the UTI incidence density and antimicrobial use.

Statistical Methods
We used the Kaplan–Meier method to analyze the time elapsing before the first UTI recurrence and the log-rank test to assess the differences in cumulative survival functions between the groups. The occurrence of all episodes of UTI was expressed in terms of incidence density, calculated by summing the number of UTI attacks and the time at risk in each group and then calculating the rate of UTI episodes per person-year at risk (PYR). Each patient contributed days at risk until the point of dropping out or receiving antimicrobials for any reason (if for UTI, at least 10 days were subtracted), or until the follow-up ended. For the children who received antibiotic prophylaxis the intervention ceased at that point. The differences in UTI incidence density between the groups were tested on the assumption that the occurrence of UTI follows a Poisson distribution. The differences between the groups in the proportion of children with at least 1 UTI recurrence, antimicrobial days per year, antimicrobial prophylaxis, and dropouts were tested with the binomial SND (Standardized Normal Deviate) test. The data were analyzed with PASW Statistics for Windows (version 18.0) and StatsDirect software (version 2.7.2).

Ethical Approval
The protocol was approved by the Ethical Committee of the Medical Faculty of the University of Oulu.

RESULTS
The baseline characteristics of the groups were similar (Table 1). Eight of the 263 children were omitted from the analysis because of protocol violation at entry, so 255 children were included in the final analyses (Figure 1). A total of 27 children (11%) dropped out: 16 (13%) in the cranberry group and 11 (9%) in the placebo group (Table 2). The most common reason was the
child’s reluctance to drink the juice (7 vs 6 children in the cranberry and placebo groups, respectively). Twenty children (16%) in the cranberry group and 28 (22%) in the placebo group had at least 1 recurrent UTI during the 12-month follow-up (Table 2). There was no significant difference in the timing of the first UTI recurrence ($P = .32$ for log–rank test; Figure 2).

A total of 74 episodes of UTI were recorded (Table 2). The UTI incidence density per PYR was significantly lower in the cranberry group, but the proportion of children having $>1$

### Table 1. Baseline Characteristics of Subjects in the Cranberry Juice and Placebo Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cranberry (n = 126)</th>
<th>Placebo (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girls</td>
<td>115 (91)</td>
<td>117 (91)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>3.8 (2.5)</td>
<td>4.5 (2.9)</td>
</tr>
<tr>
<td>No. of toddlers (aged 1–3 years)</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>Previous UTI morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of UTIs, mean (SD)</td>
<td>1.6 (1.3)</td>
<td>1.6 (1.3)</td>
</tr>
<tr>
<td>Children with at least two UTIs</td>
<td>38 (30)</td>
<td>38 (30)</td>
</tr>
<tr>
<td>Frequency of intake of berry or fruit juices$^a$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than twice a week</td>
<td>75 (61)</td>
<td>78 (62)</td>
</tr>
<tr>
<td>1–2 times a week</td>
<td>16 (13)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>32 (26)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>Frequency of intake of berries$^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>More than twice a week</td>
<td>16 (13)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>1–2 times a week</td>
<td>51 (43)</td>
<td>45 (36)</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>52 (44)</td>
<td>50 (40)</td>
</tr>
<tr>
<td>Constipation$^c$</td>
<td>2 (2)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Vesicoureteral reflux grade I–II</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Duplex system</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

All data are no. (%) unless otherwise specified.

Abbreviations: SD, standard deviation; I, urinary tract infection.

$^a$ Missing data: 3 children in the cranberry group and 6 in the placebo group.

$^b$ Missing data: 7 children in the cranberry group and 5 in the placebo group.

$^c$ Less than 3 bowel movements a week.

### Table 2. Urinary Tract Infection Recurrences and Compliance of the Subjects in the Cranberry Juice and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>Cranberry (n = 126)</th>
<th>Placebo (n = 129)</th>
<th>Difference</th>
<th>95% CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with recurrent UTI, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 episode</td>
<td>20 (16)</td>
<td>28 (22)</td>
<td>6%</td>
<td>−16% to 4%</td>
<td>.21</td>
</tr>
<tr>
<td>2 episodes</td>
<td>16</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 episodes</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 episodes</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of UTI episodes</td>
<td>27</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence density of UTI per PYR</td>
<td>0.25</td>
<td>0.41</td>
<td>−0.16</td>
<td>−.31 to −.01</td>
<td>.03</td>
</tr>
<tr>
<td>Antimicrobial days per year</td>
<td>11.6</td>
<td>17.6</td>
<td>−6</td>
<td>−7 to −5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis, no. (%)</td>
<td>4 (3)</td>
<td>7 (5)</td>
<td>−2%</td>
<td>−8% to 32%</td>
<td>.38</td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doses taken, %</td>
<td>64</td>
<td>80</td>
<td>−16%</td>
<td>−25% to −7%</td>
<td>.001</td>
</tr>
<tr>
<td>&gt;90% of doses taken, no. (%)</td>
<td>58 (46)</td>
<td>79 (62)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%−90% of doses taken, no. (%)</td>
<td>21 (17)</td>
<td>27 (21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50% of doses taken, no. (%)</td>
<td>47 (37)</td>
<td>21 (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dropouts, no. (%)</td>
<td>16 (13)</td>
<td>11 (9)</td>
<td>4%</td>
<td>−4% to 12%</td>
<td>.24</td>
</tr>
<tr>
<td>Follow-up days, mean (range)</td>
<td>111 (7–259)</td>
<td>122 (26–259)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PYR, person-year at risk; UTI, urinary tract infection.
recurrence was similar in both groups (Table 2). The children in the cranberry group had significantly fewer antimicrobial days, and antimicrobial prophylaxis was started on account of UTI recurrences in 4 of 126 cases (3%) in the cranberry group and 7 of 129 (5%) in the placebo group (Table 2). During the cranberry prevention regimen, the incidence densities of UTI were 0.36 per PYR in the cranberry group and 0.54 per PYR in the placebo group (difference, -0.18; 95% confidence interval [CI], -0.42 to .06; \( P = .15 \)), and after that the incidence densities were 0.12 per PYR in the cranberry group and 0.26 per PYR in the placebo group (difference, -0.14; 95% CI, -0.31 to .02; \( P = .09 \)).

Three of the 23 boys (cranberry 2, placebo 1) and 45 of the 232 girls (cranberry 18, placebo 27) had at least 1 recurrent UTI. The differences of proportions between cranberry and placebo groups were not statistically significant. There were a total of 3 recurrent UTI episodes among the boys (cranberry 2, placebo 1) and 71 among the girls (cranberry 25, placebo 46). Among the girls the UTI incidence density per PYR was significantly lower in the cranberry group (0.25 vs 0.46 episodes per PYR; difference, -0.19; 95% CI, -0.34 to -0.03; \( P = .02 \)). When the toddlers (aged 1–3 years) and older children were analyzed separately, the results were consistent with the whole group result but the differences between the cranberry group and placebo group were not statistically significant.

*Escherichia coli* was the dominant bacterial pathogen, found in 79% of the isolates in both groups (\( P = .96 \)). All the baseline samples were negative, and only 1 control sample had significant bacterial growth at 12 months. This child had no symptoms, however, and the growth was considered to represent asymptomatic bacteriuria and was not treated.

An average of 64% of the doses of cranberry juice and 80% of the doses of the placebo were actually taken, indicating that compliance was better among the children receiving the placebo (Table 2).

**DISCUSSION**

In the current study, regular drinking of cranberry juice reduced the number of UTI recurrences by 43% but did not significantly reduce the number of children experiencing at least 1 recurrence after the initial UTI episode. Among adults, cranberry juice has been reported to reduce both the number of patients affected and the number of episodes [10, 11, 13]. This difference can be explained by the lower-than-expected recurrence rate, because we based our sample size calculations on an expected recurrence rate of 30% by reference to earlier studies [7, 8]. In practice, however, only 22% of the control children in our trial experienced at least 1 recurrence, which was comparable to the rate of
19% recorded in a recent UTI prevention trial [5]. Even though the UTI incidence density was a secondary outcome, we believe that our figures indicate a true protective effect of cranberry juice against UTI in children comparable to that found in adults.

The preventive effect was more evident in the second half of the period concerned, a finding that is in line with the observation in our earlier trial in which cranberry-lingonberry juice maintained its protective effect against UTI for at least 6 months after the women ceased to consume it [11]. Cranberry products are thought to act against uropathogenic bacteria—mostly E. coli—by inhibiting their growth and p-pili–mediated adhesion and possibly by reducing their biofilm production [18–21]. It may be that this effect does not happen in the urinary tract but in the gut. The selection pressure created in the stool by the presence of cranberry residues may induce a shift toward a less uropathogenic bacterial flora, and hence prolonged protection against UTI. The changes in the composition of gut flora and virulence of the pathogens happen over a period of time, so the efficacy of cranberry juice in the prevention of UTI is not manifested immediately. We did not see any major changes in the colonic bacterial flora when analyzed in terms of the fatty-acid composition of the stool in our earlier study of children receiving cranberry juice [17], but this does not indicate that there cannot be changes in the ability of the bacteria to cause UTI.

The UTI recurrence rate of the children was lower than that in adults, and the recurrences were later [11]. Whereas 30% of the adult women in the control group had had at least 1 recurrence at 3 months, this figure was only 10% in the children in the placebo group [11], while at 12 months 39% and 22%, respectively, had had recurrences [11]. It seems that children develop recurrences of UTI at a constant rate over time, an observation supported by findings in other studies [5, 7]. The slower and lower UTI recurrence rate in children may be due to differences in UTI risks and pathogenesis, which are quite well characterized in adults but not so well in children [2–5, 7, 22]. Uropathogenic bacteria are able to create intravesical pods where they rest in biofilm form and cause recurrences or relapses when circumstances allow [23]. This has been suggested as an explanation for the numerous recurrences that occur in adults soon after an initial UTI. Also, VUR is common in children at the age at which they suffer from UTIs [7], whereas it disappears as the children grow up and is quite unusual in adults [24, 25]. It should also be remembered that we excluded children with grade III or higher VUR from the current trial and there was only 1 child with grade I–II VUR in each group.

Compliance in the cranberry group was not as good as in our earlier study, which lasted 3 months [17], and it was poorer than in the control group. On the other hand, it was as good or better than the compliance with the long-term antimicrobial regimen prescribed for UTI prophylaxis [5, 8]. The number of children who refused to take any juice and dropped out of the study was equal in both groups. The relatively low rate of compliance obviously detracts from the preventive efficacy of cranberry juice and its usefulness in clinical practice.

There are some shortcomings in our trial. Urinary samples were taken only when the child had symptoms suggestive of UTI, and we have data on asymptomatic bacteriuria only at the start and end of the trial. Even though asymptomatic bacteriuria is of no clinical importance, it may compromise the results by raising the number of UTI diagnoses if the child has nonspecific symptoms such as fever at the same time. The samples taken at the start and end suggest that there was only 1 child with asymptomatic bacterial growth, so that we believe that our results were not compromised by cases of asymptomatic bacteriuria. In addition, we had excluded those children who would most urgently need antimicrobial prophylaxis, because we considered it unethical to leave them without medication. These children included those with severe VUR, who are at the highest risk of UTI recurrences [7]. Thus we are not able to comment on whether cranberry juice would be appropriate for use in such cases. On the other hand, the majority of children who suffer from UTIs have no underlying urinary tract pathology and may benefit from cranberry juice.

Antimicrobial prophylaxis is of limited efficacy in preventing UTIs, and earlier trials have shown only modest benefit or no benefit at all [26–28]. The most recent large placebo-controlled trial found a modest reduction in the number of children having at least 1 recurrence in a year, from 19% to 13% (ie, a decrease of 6 percentage points, or a relative reduction of 65%), implying that 14 children had to be treated to prevent 1 case of UTI [5]. Also, long-term prophylactic antimicrobials may induce antimicrobial resistance, and it may similarly involve problems of compliance [5, 8, 28]. The use of cranberry juice for children seems to share some of these problems, such as limited efficacy and low compliance [29], but even so, cranberry juice has many advantages over antimicrobials as no prescription is needed and it does not induce antimicrobial resistance. On the contrary, antimicrobial consumption was reduced by 34%, or 6 days per patient-year, in the cranberry group.

In conclusion, taking account of the relatively innocent nature of UTI recurrences in children who do not have marked urinary tract pathology, cranberry juice seems to offer an alternative to antimicrobials for preventing UTIs in children who are susceptible to recurrences.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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