

Randomised trial of cranberry-lingonberry juice and *Lactobacillus* GG drink for the prevention of urinary tract infections in women

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Abstract

Objective To determine whether recurrences of urinary tract infection can be prevented with cranberry-lingonberry juice or with *Lactobacillus* GG drink.

Design Open, randomised controlled 12 month follow up trial.

Setting Health centres for university students and staff of university hospital.

Participants 150 women with urinary tract infection caused by *Escherichia coli* randomly allocated into three groups.

Interventions 50 ml of cranberry-lingonberry juice concentrate daily for six months or 100 ml of lactobacillus drink five days a week for one year, or no intervention.

Main outcome measure First recurrence of symptomatic urinary tract infection, defined as bacterial growth $\geq 10^5$ colony forming units/ml in a clean voided midstream urine specimen.

Results The cumulative rate of first recurrence of urinary tract infection during the 12 month follow up differed significantly between the groups ($P=0.048$). At six months, eight (16%) women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had had at least one recurrence. This is a 20% reduction in absolute risk in the cranberry group compared with the control group (95% confidence interval 3% to 36%, $P=0.023$, number needed to treat = 5, 95% confidence interval 3 to 34).

Conclusion Regular drinking of cranberry juice but not lactobacillus seems to reduce the recurrence of urinary tract infection.

Introduction

Up to 60% of women have a urinary tract infection at some point in their life.¹ At least a third of women with urinary tract infection will experience a recurrence during the following year, with recurrence being most common in the age groups 25-9 and over 55 years.²

The bacteria causing urinary tract infection arise from the stools. Dietary changes can alter the balance of faecal bacteria.³ Vaccinium berries and products containing lactobacilli have been shown to act against the coliform bacteria that cause most urinary tract infections.^{4,5} Cranberry juice prevents bacteriuria in elderly women,⁶ and locally administered lactobacilli prevent recurrences of urinary tract infections.⁷ To evaluate whether these products given orally are effective in preventing symptomatic recurrences of urinary tract infection we conducted an open, randomised, controlled trial.

Participants and methods

Study population and design

We recruited women during 1993-7 from the Finnish student health service at the University of Oulu and the occupational health centre for the staff of Oulu University Hospital. Women who had a urinary tract infection caused by *Escherichia coli* ($\geq 10^5$ colony forming units/ml in clean voided midstream urine) and were not taking antimicrobial prophylaxis were invited to participate. After giving informed consent, they were randomly allocated into three groups.

The first group received 50 ml of cranberry-lingonberry juice concentrate (Maija, Marli, Finland) a day for six months, the second group got 100 ml of *Lactobacillus* GG drink (Gefilus, Valio, Finland) five days a week for one year, and the third group served as an open control group. The cranberry-lingonberry juice contained 7.5 g cranberry concentrate and 1.7 g lingonberry concentrate in 50 ml of water with no added sugars, and the lactobacillus drink contained 4×10^{10} cfu of *Lactobacillus* GG/100 ml. Participants were advised to prepare a drinkable juice by adding 200 ml of water but no sweeteners to the 50 ml of concentrate. Both drinks were commercially available at the time.

Whenever a participant had symptoms suggesting urinary tract infection (frequency, urgency, dysuria, haematuria, nocturia, fever, or back or flank pain), we obtained a clean voided midstream urine sample for culture. The samples were cultured immediately by standard procedures, and we used $\geq 10^5$ cfu/ml as the criterion for infection. The laboratory staff were unaware as to which of the treatment groups participants belonged.

We followed perianal and urethral colonisation with lactobacilli by taking swab samples at the start and at three and 12 months. The protocol was evaluated and approved by the ethics committee of the medical faculty of the University of Oulu.

Sample size

We calculated the sample size based on the assumption that at least 30% of women will experience a recurrence of urinary tract infection within a year.² We considered a reduction in recurrences to 10% as clinically important. To detect such a reduction with a two tailed α of 0.05 and a power of 80%, we needed 70 women in each group. Recruitment had to be stopped prematurely because the cranberry juice supplier stopped producing the juice.

Statistical methods

We used the Kaplan-Meier method to analyse the cumulative first recurrence and the Breslow test to assess the differences in occurrences at the end of the study. We calculated the incidence density by adding the total number of episodes of urinary tract infection

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Baseline characteristics of the subjects in the cranberry-lingonberry juice *Lactobacillus* GG drink, and control groups. Values are numbers (percentages) of participants unless stated otherwise with percentages calculated from the number of women giving information on the question concerned

Characteristics	Cranberry (n=50)	Lactobacillus (n=49)	Control (n=50)
Age (years):			
Mean (SD) age	32 (9.8)	30 (11.8)	29 (10.5)
Aged <30	30 (60)	36 (73)	36 (72)
Aged 30-55	18 (36)	11 (22)	13 (26)
Aged >55	2 (4)	2 (4)	1 (2)
Intercourse frequency before intervention:			
Less than once a week	16 (33)	25 (51)	13 (27)
1-2 times/week	17 (35)	11 (22)	18 (38)
>3 times/week	16 (33)	13 (27)	17 (35)
Intercourse frequency during follow up:			
Less than once a week	10 (23)	9 (19)	7 (15)
1-2 times/week	19 (43)	23 (49)	20 (43)
>3 times/week	15 (34)	15 (32)	20 (43)
Used birth control during follow up*	39 (81)	39 (81)	38 (83)
Pregnancy during follow up	1 (2)	2 (4)	2 (4)
Mean No of antibiotic courses in past year	2.6	2.1	2.1
Antimicrobials for urinary tract infection in past year	44 (90)	41 (85)	41 (85)
Previous urinary tract morbidity:			
Mean (range) No of infections	6 (1-30)	6 (1-30)	6 (1-20)
Urinary tract anomalies†	3 (7)	2 (4)	0
Antimicrobial prophylaxis for urinary tract infection:			
Before intervention	10 (21)	8 (17)	5 (11)
During follow up	1 (2)	5 (10)	3 (6)
Mean (SD) daily fluid intake (l):			
At start	1.6 (0.5)	1.6 (0.6)	1.5 (0.5)
At 12 months	1.6 (0.7)	1.7 (0.7)	1.6 (0.5)

*Includes condom, coil, sterilisation, and oral contraception; no woman was using a diaphragm or spermicides.

†Includes grade II vesicourethral reflux (2), ureterocele (1), operated urethral malformation (1), and urinary incontinence (1).

and the time at risk in each group and then calculating the rate of episodes per person year at risk.

Results

A total of 150 women gave their informed consent and were randomly allocated into three groups, 50 in each. One subject in the lactobacillus group who was taking postcoital antimicrobials was excluded from the analysis. The groups were similar in their baseline characteristics with regard to the risk of urinary tract infection (table). Only 13 women dropped out of the study, usually because of moving away.

During the six months, eight (16%) women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had at least one episode of urinary tract infection. This is a 20% reduction in absolute risk in the cranberry group compared with the control group (95% confidence interval 3% to 36%, $P=0.023$, number needed to treat=5, 95% confidence interval 3 to 34). The numbers who had had a recurrence at 12 months were 12, 21, and 19 in the cranberry, lactobacillus, and control groups respectively. The cumulative first recurrence of urinary tract infection differed significantly between the groups throughout the trial ($P=0.048$ at 12 months; figure). Recurrence during the study period was significantly lower in the cranberry group than in the control group ($P=0.014$ at 6 months, $P=0.052$ at 12 months).

There were 98 episodes of urinary tract infection altogether during follow up, of which 21 (21%) occurred in the cranberry group, 39 (40%) in the lactobacillus group, and 38 (39%) in the control group. The difference of 0.36 in incidence densities per person year between the cranberry and control group was significant (95% confidence interval 0.03 to 0.68).

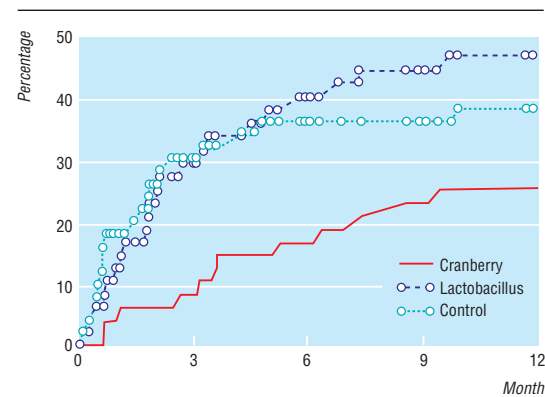
The causative bacterium was *E coli* in 80% of the episodes. The proportion of episodes caused by *E coli* did not differ between the study groups. The number of women with perianal or urethral cultures positive for lactobacilli at any time during follow up was similar in all three groups; there were 32 (71%) in the cranberry group, 33 (67%) in the lactobacillus group, and 37 (82%) in the control group.

No adverse events were reported except occasional complaints about the bitter taste of the cranberry juice.

Discussion

Our study confirms the common belief that symptomatic recurrences of urinary tract infection can be prevented with cranberry juice. In a recent review, the previous evidence for this was found inconclusive,⁸ although earlier reports had suggested a beneficial effect.⁹ The daily consumption of 300 ml of cranberry juice reduced bacteriuria in postmenopausal women, but no beneficial effect was found among children with neurogenic bladder.^{6, 10} Our study population represented a typical group of women at risk of recurrences of urinary tract infection. Such women are also the most willing and able to take preventive measures. We thus believe that our result is of both medical and practical importance.

In the United States, over 11 million women each year receive antimicrobials for urinary tract infection, costing over \$1.6bn (£1100m).¹ Antimicrobial treatment and prophylaxis has resulted in increasing resistance to antimicrobials among uropathogenic bacteria.¹¹ Cranberry juice provides an alternative tool for prevention of urinary tract infection that could result in decreased use of antimicrobials.



Cumulative rate of first recurrence of urinary tract infection during 12 month follow up in women receiving cranberry juice for six months, *Lactobacillus* GG drink for 12 months, or no intervention. The difference between groups was significant ($P=0.023$ at 6 months, $P=0.048$ at 12 months). Occurrence of urinary tract infection was significantly lower in cranberry group than in control group ($P=0.014$ at 6 months, $P=0.052$ at 12 months)

Action of cranberry juice

The berries of *Vaccinium* species such as cranberries and blueberries contain condensed tannins called proanthocyanidins. These can prevent the expression of the P fimbriae of *E coli*,⁴ which is the most common uropathogenic bacterium; its P fimbriae are thought to be the most important virulence factor in causing urinary tract infection. The blocking of fimbrial adhesion by cranberry juice prevents *E coli* and other gram negative bacteria from colonising the uroepithelial cells.¹²⁻¹⁴ The juice may help to prevent urinary tract infection either by selecting less adhesive bacterial strains in the stool or by directly preventing *E coli* from adhering to uroepithelial cells, or by both of these mechanisms.^{15, 16} Our finding of no increase in recurrences after stopping cranberry prophylaxis supports the theory of bacterial selection in the stool.

Lactobacillus

The lactobacillus drink had no effect on urinary tract infection, possibly because we were unable to induce lactobacilli colonisation of the periurethral area. Lactobacilli have been shown to colonise the human intestine at doses of 10⁸⁻¹⁰ cfu/day and to replace other bacterial species, especially coliform bacteria.^{5, 17} Consumption five times a week may have been too infrequent. Intravaginal administration of lactobacilli has been found to reduce the number of coliform bacteria in the periurethral area and the number of urinary tract infections after antimicrobial treatment.⁷ In postmenopausal women, vaginal lactobacilli are replaced by enterobacteriaceae, increasing the risk of bacteriuria. This process can be reversed by intravaginal administration of oestriol.¹⁸

Validity

We had to stop our trial prematurely because the manufacturer of the cranberry juice stopped producing it. However, the difference in the occurrence of urinary tract infection between the cranberry and control group was clear and constant even in this limited sample size. A compliance follow up sheet was returned by only half of the subjects, but the reports suggested that the compliance was good and the stratified analysis showed no differences between the subjects who did and did not return the follow up sheet.

In conclusion, the daily consumption of 50 ml of cranberry-lingonberry concentrate reduced recurrences of symptomatic urinary tract infection in women by about half, whereas the lactobacillus drink was ineffective. Since cranberry juice is a natural food product and readily available, it seems a useful means for self administered prevention of urinary tract infection.

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Contributors: MU initiated and coordinated the formulation of the primary study hypothesis. TK participated in the formulation of study hypothesis and design and was responsible for coordinating the collection and entry of data. KS was responsible for the recruitment of the study subjects in the Finnish student health service. MU, MN, KS, and TK discussed core ideas, designed the study protocol, and participated in the data analysis, interpretation of the results, and writing the paper. TP was responsible for the statistical analysis, participated in the interpretation of the results, and contributed to the design and

What is already known on this topic

Up to 60% of women will have a urinary tract infection and a third of them will have several recurrences

Vaccinium berries and products containing lactobacilli may affect the coliform bacteria that cause urinary tract infection

What this study adds

50 ml of cranberry-lingonberry juice concentrate daily reduced recurrences of symptomatic urinary tract infection by about half compared with the control group

Lactobacillus GG drink had no effect on recurrence

writing the paper. MK was responsible for the quality of the laboratory analysis and contributed to the design and the writing of the paper. MU and TK are guarantors of the content of the paper.

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- 1 Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. *Ann Epidemiol* 2000;10:509-15.
- 2 Ikäheimo R, Siitonen A, Heiskanen T, Kärkkäinen U, Kuosmanen P, Lipponen P, et al. Recurrence of urinary tract infection in a primary care setting: analysis of a 1-year follow-up of 179 women. *Clin Infect Dis* 1996;22:91-9.
- 3 Gibson GR. Dietary modulation of the human gut microflora using prebiotics. *Br J Nutr* 1998;80:209-12.
- 4 Howell AB, Vorsa N, Der Marderosian A, Foo LY. Inhibition of the adherence of P-fimbriated *Escherichia coli* to uroepithelial-cell surfaces by proanthocyanidin extracts from cranberries. *N Engl J Med* 1998;339:1085-6.
- 5 Chan RC, Reid G, Irvin RT, Bruce AW, Costerton JW. Competitive exclusion of uropathogens from human uroepithelial cells by *Lactobacillus* whole cells and cell wall fragments. *Infect Immun* 1985;47:84-9.
- 6 Avorn J, Monane M, Gurwitz JH, Glynn RJ, Chodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. *JAMA* 1994;271:751-4.
- 7 Reid G, Bruce AW, Taylor M. Influence of three-day antimicrobial therapy and lactobacillus vaginal suppositories on recurrence of urinary tract infections. *Clin Ther* 1992;14:11-6.
- 8 Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. *Cochrane Database Syst Rev* 2000;2:CD001321.
- 9 Blanderwick NR. The specific role of foods in relation to the composition of the urine. *Arch Intern Med* 1914;14:409-50.
- 10 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;135:698-702.
- 11 Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA* 1999;281:736-8.
- 12 Schmidt DR, Sobota AE. An examination of the anti-adherence activity of cranberry juice on urinary and non-urinary bacterial isolates. *Microbios* 1988;55:173-81.
- 13 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 Chemother* 1989;33:92-8.
- 14 Ahuja S, Kaack B, Roberts J. Loss of fimbrial adhesion with the addition of *Vaccinium* macrocarpon to the growth medium of P-fimbriated *Escherichia coli*. *J Urol* 1998;159:559-62.
- 15 Sobota AE. Inhibition of bacterial adherence by cranberry juice: potential use for the treatment of urinary tract infections. *J Urol* 1984;131:1013-6.
- 16 Ofek I, Goldhar J, Zafriri D, Lis H, Adar R, Sharon N. Anti-*Escherichia coli* adhesin activity of cranberry and blueberry juices. *N Engl J Med* 1991;324:1599.
- 17 Saxelin M, Pessi T, Salminen S. Fecal recovery following oral administration of *Lactobacillus* strain GG (ATCC 53103) in gelatine capsules to healthy volunteers. *Int J Food Microbiol* 1995;25:199-203.
- 18 Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. *N Engl J Med* 1993;329:753-6.

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