Does ingestion of cranberry juice reduce symptomatic urinary tract infections in older people in hospital? A double-blind, placebo-controlled trial


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Abstract

Background: cranberry juice is often given to older people in hospital to prevent urinary tract infection (UTI), although there is little evidence to support its use.

Objective: to assess whether cranberry juice ingestion is effective in reducing UTIs in older people in hospital.

Design: randomised, placebo-controlled, double-blind trial.

Setting: Medicine for the Elderly assessment and rehabilitation hospital wards.

Subjects: 376 older patients in hospital.

Methods: participants were randomised to daily ingestion of 300 ml of cranberry juice or matching placebo beverage. The primary outcome was time to onset of first UTI. Secondary outcomes were adherence to beverage drinking, courses of antibiotics prescribed, and organisms responsible for UTIs.

Results: a total of 21/376 (5.6%) participants developed a symptomatic UTI: 14/189 in the placebo group and 7/187 in the cranberry juice group. These between-group differences were not significant, relative risk (RR) 0.51 [95% CI 0.21–1.22, P=0.122]. Although there were significantly fewer infections with Escherichia coli in the cranberry group (13 versus 4) RR 0.31 [95% CI 0.10–0.94, P=0.027], this should be interpreted with caution as it was a secondary outcome.

Conclusion: despite having the largest sample size of any clinical trial yet to have examined the effect of cranberry juice ingestion, the actual infection rate observed was lower than anticipated, making the study underpowered. This study has confirmed the acceptability of cranberry juice to older people. Larger trials are now required to determine whether it is effective in reducing UTIs in older hospital patients.

Keywords: urinary tract infection, randomised clinical trial, cranberry juice, hospital, elderly

Introduction

Although cranberry juice is commonly given to older people to prevent urinary tract infection (UTI), there is little evidence to support its use. Only one large trial to date has studied the effect of cranberry juice in older people. Avorn and colleagues randomised 153 elderly women from housing complexes in a controlled trial using a matching placebo. Ingestion of 300 ml of cranberry juice daily for 6 months was associated with a lower incidence of bacteriuria with pyuria [1]. However, analysis was not by intention to treat and substantially more of the placebo group (25%) than the cranberry group (7%) had a history of UTI in the 6 months prior to the study. This has led to criticism of the randomisation or blinding employed [2]. Furthermore, as asymptomatic bacteriuria is a condition which does not require
treatment, there seems little value, even if cranberry juice is effective in preventing it.

The mechanism by which an effect of cranberry might be mediated has been the source of much debate. Berries of the *Vaccinium* species, such as cranberries and blueberries, contain tannins called proanthocyanidins. Proanthocyanidins are stable phenolic compounds, which exhibit potent anti-adhesion activity against both sensitive and resistant strains of *P-fimbriated Escherichia coli*, preventing adherence to uroepithelial cells which line the wall of the bladder [3].

Cranberry juice is an attractive therapy as it is a cheap, natural product which should not lead to antibiotic resistance. Given that UTI occurs more frequently in old age than at any other time of life [4], and is common in hospitalised older people, this study was designed to examine whether ingestion of cranberry juice was associated with a reduction in symptomatic UTIs in elderly hospital patients.

**Methods**

**Study population**

In contrast to other studies of cranberry juice and UTI, the target population was older hospital patients, not those with a history of recurrent UTIs.

**Inclusions:** Patients aged 60 years or over admitted to either acute Medicine for the Elderly assessment or rehabilitation units (Royal Victoria Hospital, Ashludie Hospital, Ninewells Hospital, Dundee and Perth Royal Infirmary) for elderly people in Tayside, Scotland.

**Exclusions:** Mental State Questionnaire (MSQ) score <5/10; dysphagia; symptoms of a UTI; antibiotic treatment; anticipated length of stay less than 1 week; regular drinkers of cranberry juice; presence of an in-dwelling catheter; and terminal illness. In light of a UK Committee on Safety of Medicines alert about a potential interaction between cranberry juice and warfarin which emerged during the final 8 weeks of recruitment, warfarin was added as an exclusion for that period only [5].

Written informed consent was obtained from participants and the study was approved by the Tayside Committee on Medical Research Ethics. Potential participants were given the opportunity to taste a sample of the juice prior to giving consent.

**Randomisation**

Participants were stratified by gender and by hospital and randomised to receive either 150 ml of cranberry juice or 150 ml of placebo beverage twice daily. To optimise adherence, the juice was prescribed in the ward drug kardex and administered by nursing staff. Randomisation was performed by opening sealed envelopes in numbered sequence prepared by an individual not otherwise involved in the study, and prepared from a computer-generated random numbers program.

The treatment code was held in a sealed envelope by the Clinical Trials Pharmacist, The Pharmacy, Ninewells Hospital.

**Cranberry juice and placebo juice**

Both beverages looked and tasted identical. Both the Light Cranberry low calorie juice and the matching placebo beverage were provided by Ocean Spray Cranberries, Inc. (Lakeville-Middleboro, MA, USA) and produced annually by Gerber Foods Soft Drinks Ltd (Bridgewater, Somerset, UK). The juice contained water, cranberry juice from concentrate (25%), sugar, vitamin C and a non-nutritive sweetener (aspertame). The cranberry concentrate used to produce the juice had a proanthocyanidin concentration of 11.175 µg/g (dry solids basis). The placebo beverage contained no cranberry solids, but contained water, sugar (sucrose), elderberry extract, quinic acid, citric acid, malic acid, vitamin C and non-nutritive sweetener (aspertame).

**Urinalysis methods**

Clean catch urine samples were taken and sent on a ‘Dipslide’ (Medical Wire & Equipment Co. (Bath) Ltd) to the microbiology laboratory for culture. Patients who displayed symptoms or signs of UTI (i.e. frequency, dysuria, or a non-specific deterioration in clinical condition) and in whom ward-based urine dip stick tests found the presence of leucocyte esterase and/or nitrates were cultured. Only pure growths of greater than or equal to 10^4 colony-forming units per ml (cfu/ml) were reported with an antibiotic sensitivity. Two or more strains were regarded as mixed growths and repeat samples requested. Given the age of the population and the practical difficulties of obtaining such urine specimens, no restriction was put on the amount of time the urine had to be in the bladder before sampling.

**Outcome measures**

**Primary outcome**

All outcomes were assessed by an individual who was blind to treatment group. The primary outcome was time to onset of first symptomatic UTI. This was defined as a culture-positive urine growing a single organism of greater than 10^4 cfu/ml urine specimen [6].

**Secondary outcomes**

**Courses of antibiotics prescribed.** All courses of antibiotics prescribed for any indication were noted to assess any potential impact of cranberry juice ingestion on antimicrobial use.

**Adherence.** The beverages were prescribed by the ward doctor in the ward drug kardex, and the amount consumed was recorded daily by ward nursing staff on an adherence sheet.

**Responsible organisms.** The Dipslides were incubated in air at 37°C overnight. Pure cultures of greater than 10^4 cfu/ml of urine were identified using the VITEK 1 (Biomerieux). Cultures with less than 10^4 cfu/ml were reported as ‘no significant growth’ or ‘no growth’ accordingly. Cultures with more than a single colony type were reported as ‘mixed growth – suggestive of contamination’.

**Other information**

**History of positive urine culture**

Participants’ microbiology results were examined for the 12 months prior to admission using the computerised regional reporting system, to determine the number of
positive urine culture specimens received by the local microbiology laboratory during that period.

Follow-up

Participants were followed up for 35 days following randomisation or until hospital discharge. Withdrawals were censored at hospital discharge or at occurrence of first symptomatic UTI. All adverse events and reasons for withdrawal were noted.

Statistical methods

Sample size

Based on local pilot data, it was predicted that a final sample of 380 participants would be required to have 80% power at $P < 0.05$ of detecting a reduction in the proportion of patients having at least one episode of UTI in the cranberry juice group to 11% compared to 22% in the control group. Anticipating a dropout rate of 15%, we aimed to recruit 440 patients, to give a final evaluable sample of 380.

Statistical analysis

Data were entered onto Excel database and analysed using SPSS version 11.5. Full statistical analysis was performed prior to breaking the treatment code. Analysis was by intention to treat. Between-group comparisons were made using the unpaired t-test for normally distributed variables. Categorical variables were compared using the Chi squared test. Time to first episode of infection is presented as a Kaplan–Meier curve and differences between groups were assessed using the log rank test.

Results

A total of 3,228 patients were admitted to the study wards during the trial period, and the reasons for exclusion are given in the participant recruitment and follow-up chart in Figure 1. The reasons for potential participants failing to meet the inclusion criteria were: significant cognitive impairment with MSQ score of less than five out of ten, 530/2,238 (23.6%); the presence of a urinary catheter, 384/2,238 (17.1%); anticipated hospital stay of less than 1 week, 315/2,238 (14.1%); being terminally ill, 263/2,238 (11.7%); symptomatic UTI, 111/2,238 (4.9%); dysphagia, 106/2,238 (4.7%); regular cranberry juice drinkers, 71/2,238 (3.2%); respite admission, 63/2,238 (2.8%); on antibiotic therapy, 39/2,238 (1.7%); not assessed, 174/2,238; and other, 182/2,238. Of the 501 who were eligible to participate, 158/501 (31.5%) cited dislike of the taste of the juice as their reason for declining.

Only 376 participants were randomised compared to the target of 440 as a consequence of changes in ward organisation and a reduction in subsequent patient throughput. Participants were similar at baseline with no significant differences between the groups (Table 1). Between 25 and 28% had a history of culture-positive urine in the previous 12 months. Participants in the placebo group were observed for a
median [inter-quartile range (IQR)] of 21 [22] days, and those in the cranberry juice group were observed for 24 [23] days (P=0.999 Mann–Whitney test.) The placebo beverage was consumed for a median [IQR] of 15 [18.5] days, and cranberry juice for 16 [26] days (P=0.574).

Primary outcome
A total of 21/376 (5.6%) patients had at least one symptomatic UTI (14 in the placebo group and 7 in the cranberry juice group); relative risk (RR) 0.51 [95% CI 0.21–1.22, P=0.122). Of these, antibiotic therapy was initiated in 14/21 (67%), 8 in the placebo group and 6 in the cranberry juice group. No significant differences were found between treatment groups, although the cranberry juice group had fewer infections. A Kaplan–Meier plot of the proportion of participants free from symptomatic UTI shows a similar initial infection rate, but the curves begin to separate after 15 days (Figure 2).

One patient in the placebo group was treated with an antibiotic for a UTI, but as no confirmatory urine culture was obtained, this individual’s results were excluded from the analysis.

Table 1. Baseline characteristics (n=376)

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Cranberry juice group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (sd) age</td>
<td>81.4 (7.6)</td>
<td>81.3 (7.3)</td>
</tr>
<tr>
<td>Males/females</td>
<td>56/133</td>
<td>65/122</td>
</tr>
<tr>
<td>Median (range) number of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>medications per day</td>
<td>8 (1–19)</td>
<td>7 (1–20)</td>
</tr>
<tr>
<td>History of culture-positive urine in past 12 months, n (%)</td>
<td>48 (25%)</td>
<td>53 (28%)</td>
</tr>
</tbody>
</table>

*^46 values missing from number of medications.*

Adherence
Median [IQR] adherence from a maximum of 300 ml per day was good at 300 [44] ml for the placebo beverage and 300 [28] ml for the cranberry juice (P=0.208, Mann–Whitney test). Adherence data were missing on 11/376 (2.9%) of participants, 5 from the placebo group and 6 from the cranberry juice group.

Antibiotic use
A total of 35/189 (19%) of participants in the placebo group were prescribed antibiotics for any indication during the period of observation, compared to 32/187 (17%) of the cranberry juice group (P=0.721). The median (range) duration of antibiotic treatment was 7 (1–19) days and 7 (1–15) days, respectively.

Adverse events
Only 13 adverse events occurred and all resulted in withdrawal from the study. The six in the placebo group comprised two deaths and four episodes of gastrointestinal upset. The seven in the cranberry group comprised three deaths, two episodes of gastrointestinal upset, one episode of skin redness and itching, and one elevated blood glucose level in a known diabetic patient.

Withdrawals
There were 115/376 (30%) withdrawals from the study (62 from the placebo group and 53 from the cranberry juice group), and reasons for withdrawal were similar between groups. The commonest reason for withdrawal was a desire not to continue with the study (25/189 in the placebo group and 23/187 in the cranberry group). Only 13/189 and 12/187 cited dislike of the beverage as the reason for withdrawing, and urinary catheterisation led to withdrawal of 11/189 and 7/187 in the placebo and cranberry groups, respectively.

Responsible organisms
Examining all 21 infections, E. coli was responsible for 13 of the infections in the cranberry group, but only 4 in the cranberry group. This between-group difference was significant, RR 0.31 [95% CI 0.10–0.94, P=0.027] Chi squared test.

Discussion
Despite having the largest sample size of any clinical trial of cranberry juice ingestion to date, this study still emerged as underpowered to detect a difference between the groups in time to onset of first symptomatic infection. The rate of UTI observed in the placebo group (7.4%) was considerably lower than in our open pilot study, and much lower than the rates of 36% and 32% reported in longer term studies of
younger women with a history of recurrent UTI [7, 8]. There is little in the literature on what the expected rate of UTI might be in elderly hospital patients. This is due to several factors: confusion about the distinction between asymptomatic bacteriuria and symptomatic infection [9]; differences in the bacteriological features of UTI in old versus young patients; and a lack of clarity on the definition of symptomatic UTI in elderly people. Given the rates of symptomatic UTI observed, we would have required 574 participants per group to have 80% power of detecting a difference at \( P=0.05 \). In reality with the sample size we had of 188 per group, we had less than 50% power to detect a significant difference between the groups.

\textit{Escherichia coli} was the commonest organism isolated in our study, and is recognised as the most common urinary tract pathogen on elderly people [10]. We found significantly fewer infections with \textit{E. coli} in the cranberry juice group than in the control group. This was only a secondary outcome, but the observation is consistent with there being an effect of cranberry juice. An important reason for evaluating the effectiveness of cranberry juice is because of its potential to reduce antibiotic prescriptions, and hence antimicrobial resistance.

Our trial differs in a number of respects from the two recent positive trials of cranberry juice [7, 8]. The study sample in both these trials were 150 young women (mean age 32 and 43 years, respectively) with a history of UTI, and cranberry product was taken for a period of between 6 months and 1 year. This duration of treatment is considerably longer than the mean of 18 days of beverage consumption in our trial. There is good evidence from \textit{in vitro} work that the anti-adhesion activity of cranberry juice on fimbriated \textit{E. coli} is present in the urine 2 hours after ingestion, and that it persists for 10 hours following ingestion [11], making it plausible that our regime of twice daily ingestion for 18 days might be effective in reducing episodes of infection. An updated Cochrane review which incorporates these trials concludes that cranberry juice ‘may decrease the number of symptomatic UTIs over a 12 month period in younger women’ [12].

Our trial had a number of methodological strengths, addressing many of the criticisms of the existing literature [12]. Firstly, analysis was by intention to treat. Secondly, it was the only trial other than Avorn’s to have used a matching placebo beverage [1]. Thirdly, it targeted a previously unstudied group—elderly hospital patients—a group at high risk of UTI. Fourthly, it included male participants, a group in whom the effectiveness of cranberry juice has yet to be established. And finally, high adherence levels of around 90% were achieved by having the beverages prescribed in the ward drug kardex and so administered twice daily by nursing staff, who also documented the quantity unconsumed. This is a considerably more robust method than self-report which has been used in previous studies. The high number of withdrawals in previous cranberry juice trials has been raised as a concern, but the adverse events rate in our trial was low, and did not differ significantly between groups. Only 25/376 (6.6%) withdrew citing a dislike of the beverage as the reason.

This is the largest randomised trial yet to have examined the effect of cranberry juice ingestion on symptomatic UTI rates, and the only one to have participants of both sexes. The observed symptomatic infection rate was considerably lower than anticipated so the study was accordingly underpowered. Whilst inconclusive, the results are in keeping with other studies of cranberry juice in showing a 50% difference between groups in UTI incidence [1, 7, 8]. Although this study has confirmed the acceptability and tolerability of cranberry ingestion in older people, larger trials are now required to establish whether cranberry juice ingestion is effective in the prevention of UTI in elderly hospital patients.

**Key points**

- Cranberry juice is commonly given to older people in hospital to prevent UTI, although there is little evidence to support its use.
- Despite having the largest sample size of any clinical trial of cranberry juice to date, the actual UTI rate was lower than anticipated, making the study underpowered and inconclusive.
- Significantly fewer infections with \textit{E. coli} occurred in the cranberry juice group, a finding compatible with an effect of the juice. However, this was a secondary outcome, so should be treated with caution.

**Acknowledgements**

The study was funded by project grant K/OPR/2/2/D398 from the Chief Scientist Office at the Scottish Executive Department of Health. The cranberry juice and matching placebo were supplied by Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA, USA. Thanks to the ward staff, the laboratory staff in medical microbiology and the study participants.

**Conflict of interest**

None declared.

**References**

Effectiveness of an alternating pressure air mattress for the prevention of pressure ulcers

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Abstract

Background: studies of the effectiveness of alternating pressure air mattresses (APAMs) for the prevention of pressure ulcers are scarce and in conflict.

Objective: evaluating whether an APAM is more or equally effective as the standard prevention.

Design: randomised controlled trial.

Setting and subjects: patients admitted to 19 surgical, internal, or geriatric wards in seven Belgian hospitals were included if they were in need of prevention of pressure ulcers. To define this need, two methods were used randomly: the Braden Scale or the presence of non-blanchable erythema (NBE).

Methods: 447 patients were randomised into either an experimental or a control group. In the experimental group, 222 patients were lying on an APAM (Alpha-X-Cell®, Huntleigh Healthcare, UK). In the control group, 225 patients were lying on a visco-elastic foam mattress (Tempur®, Tempur-World Inc., USA) in combination with turning every 4 hours. Both groups had identical sitting protocols.

Results: there was no significant difference in incidence of pressure ulcers (grade 2–4) between the experimental (15.6%) and control group (15.3%) (P=1). There were significantly more heel pressure ulcers in the control group (P=0.006). There was an interaction effect between the risk assessment method and preventive measures for the development of all pressure ulcers and sacral pressure ulcers.

Conclusion: fewer patients developed heel pressure ulcers on an APAM. Patients identified as being in need of prevention based on the presence of NBE had a tendency to develop fewer pressure ulcers on an APAM. Patients identified as being in need of prevention, based on the Braden Scale, appeared to develop more sacral pressure ulcers on an APAM.

Keywords: decubitus ulcer, prevention and control, randomised controlled trial, beds, elderly