

## ORIGINAL ARTICLE

**Effectiveness of a cranberry (*Vaccinium macrocarpon*) preparation in reducing asymptomatic bacteriuria in patients with an ileal enterocystoplasty**

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*Department of Urology, Hospital Foch, Suresnes, France***Abstract**

**Objective.** Bacteriuria is a usual complication of enterocystoplasty following cystectomy. Cranberry products may decrease the number of urinary tract infections because of a non-dialysable compound, a condensed tannin, the proanthocyanidin (PAC) type A. This study determined the effectiveness of treatment with a cranberry preparation highly dosed in proanthocyanidin A in prevention of repeated bacteriuria in patients with an ileal enterocystoplasty. **Material and methods.** Between November 2004 and November 2009, a controlled study was open to patients seen in consultation for follow-up after a radical cystectomy and ileal cystoplasty. Patients had a history of repeated urinary infection and/or bacteriuria during the pretreatment phase. During the treatment phase, patients received a cranberry (*Vaccinium macrocarpon*) preparation highly dosed in proanthocyanidin A (36 mg measured by the dimethylaminocinnamaldehyde method), one capsule a day. The primary endpoint was the absence of bacteria in urine culture. The secondary endpoints were the presence or absence of symptoms (pain, fever), continence status and upper excretory tract enlargement. Each patient was his or her own historical control. **Results.** Fifteen patients were included. The median duration of the period without treatment with cranberry compound was 18.5 (1–93) months. The median duration of the period with treatment with cranberry compound was 32.8 (13–60) months. There was a significant decrease in the number of positive urine cultures during cranberry compound treatment. **Conclusions.** Treatment with a cranberry compound seems to be effective in reducing asymptomatic bacteriuria in patients with an ileal enterocystoplasty. These results need to be validated by further double-blind randomized studies.

**Keywords:** *Bacteriuria, cranberry, cystectomy, enterocystoplasty, incontinence.*

**Introduction**

Bacteriuria is a usual complication of enterocystoplasty following cystectomy and its frequency has been assessed as being from 8% to 57% [1–3]. Bacteriuria is most often asymptomatic, but can lead to pyelonephritis and could change the properties of the neobladder wall and cause urinary incontinence [4].

A Cochrane Library review published in 2008 reported that there is some evidence that cranberry products may decrease the number of urinary tract infections (UTIs) over a 12-month period. Their effectiveness in other groups is less certain [5]. Cranberry compounds inhibit the adherence of *Escherichia*

*coli* to uroepithelial cells, the first and necessary step of UTI. This competitive inhibition is due to a non-dialysable compound, a condensed tannin, proanthocyanidin (PAC) type A. Cranberry contains a high proportion of PAC A, unlike other berries. Only PAC A is able to inhibit *E. coli* adhesion through inactivation of pili type P. There are three species of cranberry: *Vaccinium macrocarpon* is the only one to contain PAC A. The other two (*Vitis idea* and *Vitis oxycoccus*) do not contain PAC A and thus are unable to inhibit *E. coli* adhesion [6].

The aim of this preliminary pilot study was to test the effectiveness on UTIs of treatment with a cranberry (*V. macrocarpon*) preparation highly dosed in

PAC A [36 mg measured by the dimethylaminocinnamaldehyde (DMAC) method] in patients with an ileal enterocystoplasty.

## Material and methods

This is a preliminary pilot study measuring the impact of a treatment period with cranberry compound compared with a historical period without that regimen. Each patient was considered his or her own control.

The study was opened to patients seen between November 2004 and November 2008 for follow-up after a radical cystectomy and bladder replacement. The inclusion criteria were: (i) patients with a radical cystectomy (radical cystoprostatectomy for males) with urinary diversion by a Z enterocystoplasty performed in the Department of Urology, Hospital Foch [7]; and (ii) repeated urinary infections (at least two episodes) and/or bacteriuria with a significant count of colony-forming units ( $\geq 10^5$ ) characterized by urine culture. Intermittent bladder catheterization was an exclusion criterion.

Before inclusion, cultures of urine and clinical examinations were performed routinely every 3 months the first year after cystectomy and every 6 months thereafter. During the intervals, these tests were also performed in case of urinary symptoms or fever.

Once included, patients were treated with antibiotics according to the result of their urine culture. Treatment with the cranberry compound (Urell<sup>®</sup> in Europe, Ellura<sup>™</sup> in the USA) was introduced after antibiotic treatment, when urine cultures became sterile. Patients were reviewed every 3 months. Clinical data and history of UTI treatment before and during treatment with cranberry were recorded. After enterocystoplasty, urine cultures were performed every 3 months and the patient received antibiotic therapy according to the results of urine culture only in the event of symptoms. The time between cystectomy and the repeated UTIs and/or bacteriuria was defined according to the date of the first positive urine culture postoperatively. The primary endpoint of the study was the absence of bacteria in urine culture proved by a significant count of colony-forming unit ( $\geq 10^5$ ) characterized by urine culture [8]. The secondary endpoints were the presence or absence of symptoms (pain, fever), continence status and upper excretory tract enlargement. Body mass index and residual urine volume after voiding were also registered.

Qualitative and quantitative variables were compared using chi-square and Student statistical analyses. A difference was considered significant when  $p$  was less than 0.05.

## Results

Fifteen patients (13 men, 2 women), aged  $68 \pm 9$  years were included. Patients underwent radical cystectomy with orthotopic bladder replacement between September 1998 and September 2008. The mean age when radical cystectomy was performed was  $64 \pm 11$  years. The infectious episodes during the two periods of observations for all patients are described in Table I. The median time between cystectomy and the beginning of repeated UTIs and/or bacteriuria was 7.3 months (1–86 months). The median duration of period without treatment with cranberry compound was 18.5 months (1–93 months). The median duration of the period with treatment with cranberry compound was 32.8 months (13–60 months). The mean body mass index was  $26.7 \pm 3.0$  kg/m<sup>2</sup>. Two patients had type 2 diabetes. One patient had a residual urine volume measured as 300 ml before treatment and 200 ml after treatment.

There was a significant decrease in the number of positive urine cultures during cranberry compound treatment. Before treatment, all patients had repeated positive urine cultures, with *E. coli* in 86.8%, *Klebsiella pneumoniae* in 6.6% and *Pseudomonas aeruginosa* in 6.6% of cases. During treatment, only one patient (6.6%) had a positive urine culture for *Enterococcus faecalis*. There was a significant decrease in the rate of symptoms and urinary incontinence during treatment. All results are presented in Table II.

## Discussion

Bacteriuria is common when bowel is used as the material for urinary diversion because the ileal epithelium lacks inhibitory action against bacterial adherence. The intestine normally exists in symbiosis with bacteria, with no inflammatory reaction [9]. Therefore, urine in an intestinal neobladder is less bacteriostatic than urine in a native bladder. The adhesion mechanisms of *E. coli* to the cells of the intestinal wall appear to be the same as those involved in adherence to the urothelium [10]. A significant decrease in bacterial adherence was noted after the consumption of cranberry. Howell et al. showed that cranberry inhibits the adherence of p-fimbriated *E. coli* to bladder epithelial cells [11]. Thus, there was a rationale for treating bacteriuria with cranberry compound.

The utility of antibiotics for patients with an intestinal neobladder and significant bacteriuria has been debated. Wood et al. recommended not treating asymptomatic patients with a positive urinary culture

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Table I. Infectious episodes during the two periods of observations for all patients.

Patient	Period without treatment			Period with treatment		
	No. of urinary cultures taken	No. of positive urinary cultures	No. of symptomatic infections	No. of urinary cultures taken	No. of positive urinary cultures	No. of symptomatic infections
1	27	14	0	21	0	0
2	20	12	0	18	0	0
3	12	7	5	8	0	0
4	17	11	0	11	0	0
5	16	12	6	9	0	0
6	6	4	0	19	0	0
7	8	3	0	20	0	0
8	9	2	0	18	0	0
9	9	3	0	16	0	0
10	18	10	6	7	0	0
11	13	5	0	6	1	0
12	10	3	2	8	0	0
13	7	4	0	6	0	0
14	5	4	0	6	0	0
15	5	4	0	4	0	0

Table II. Results of endpoints before and during treatment with cranberry preparation.

	Before treatment	During treatment	<i>p</i>
Patients with positive urinary culture	15 (100%)	1 (6.6%)	<0.0001
Patients with symptoms (pain, fever)	4 (26.6%)	0 (0%)	0.03
Urinary incontinence	9 (60.0%)	2 (13.3%)	0.03
Night-time urinary incontinence	11 (73.3%)	6 (40.0%)	ns
Upper excretory tract enlargement	2 (13.3%)	1 (6.6%)	ns
No. of day-time urinations	6.4 ± 1.3	6.4 ± 0.5	ns
No. of night-time urinations	2.7 ± 0.9	2.2 ± 0.6	ns

ns = not significant.

211 result unless they were affected by recurrent urinary  
 212 infections [12]. Conversely, Studer et al. recom-  
 213 mended prescribing antibiotics to patients with an  
 214 intestinal neobladder and a positive urine culture  
 215 result, even if they were asymptomatic [13]. This  
 216 author has demonstrated that ureteroileal strictures  
 217 were correlated with UTI [14]. The present study  
 218 showed that bacteriuria was correlated with inconti-  
 219 nence in patients with ileal enterocystoplasty.  
 220 Recently, Zehnder et al. reported the same finding  
 221 in 48 patients with ileal bladder substitutes [15].  
 222 Other authors have shown that asymptomatic bacte-  
 223 riuria was associated with an increased risk of urinary  
 224 incontinence [4]. These results are in favour of

225 treatment of asymptomatic bacteriuria in patients  
 226 with enterocystoplasty.

227 Antibiotics could select resistant bacteria and could  
 228 modify the long-term microbial ecology. The overall  
 229 cause of increasing antibiotic resistance is selective  
 230 pressure by antimicrobial substances [16]. Repeated  
 231 antibiotic treatments for urinary infections lead to the  
 232 emergence of bacteria that are resistant to antibiotics.  
 233 Low-dose antibiotic prophylaxis in uncomplicated  
 234 recurrent urinary infection does not fall within the  
 235 mutant selection window and thus theoretically should  
 236 not cause the emergence of resistance. However, the  
 237 emergence of antibiotic-resistant pathogens may be  
 238 underestimated [16]. Conversely, cranberry has not

been incriminated in the selection of resistant bacteria. Moreover, the activity of the PAC on the inhibition of *E. coli* adhesion has been demonstrated on both antibiotic-susceptible and antibiotic-resistant bacteria [17]. In addition, no side-effects were reported with the consumption of cranberry compounds.

The design of this study limited the bias of inter-individual variations. However, the modest level of evidence of the results requires confirmation by a randomized, double-blind study.

The choice of drug was justified by the results of previous studies, which showed that the optimal dosage of *V. macrocarpon* is 36 mg/day [5]. Urell (Ellura in the USA) was the only pharmaceutical preparation with this dosage commercially available in France. In the prophylactic use of cranberry compound, the compliance of patients is lower for juice than for capsules or pills. Moreover, for daily use, the cost-effectiveness of pills is better than for juice [18].

In conclusion, treatment with a cranberry compound seems to be effective in reducing asymptomatic bacteriuria in patients with an ileal enterocystoplasty. Contrary to antibiotic treatment, cranberry has the advantage of not selecting resistant bacteria and thus preserving the bacterial ecology. In the authors' experience, asymptomatic bacteriuria was reduced by 93% during treatment, and symptoms and urinary incontinence decreased. These results need to be validated by further double-blind randomized studies.

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