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Cranberry supplementation in the prevention of non-severe lower urinary tract infections: a pilot study

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Abstract. – OBJECTIVE: Cranberry extracts have been tested as a nutritional supplementation in the prevention of recurrent lower-urinary tract infections (R-UTIs), with mixed results. This pilot, registry study evaluates the prophylactic effects of oral supplementation with a new well-standardized cranberry extract in patients with R-UTI, over a 2-month follow-up.

PATIENTS AND METHODS: All subjects were suggested to take one capsule containing a cranberry extract (Anthocran™) for 60 days and were also given lifestyle advice. Clinical outcomes were compared between patients on cranberry extracts and those who did not take this supplementation.

RESULTS: In total, 22 subjects completed the study in each of the two groups. In the cranberry group, the reduction in the frequency of UTI episodes during the study period compared with the two months before the inclusion was 73.3% ($p < 0.05$). This figure was 15.4% in the control group ($p < 0.05$; $p = 0.012$ vs cranberry group). Seven (31.8%) subjects in the cranberry group were symptom-free; no patient was symptom-free in the control group ($p < 0.05$). The mean duration of UTI episodes was 2.5±1.3 days in the cranberry group, compared with 3.6±1.7 days in subjects not on cranberry ($p < 0.05$). Three subjects (13.6%) in the cranberry group and 8 (36.3%) in the control group required medical consultation for UTI symptoms ($p < 0.05$). Urine evaluation was completely negative in 20/22 subjects in the Cranberry group (90.9%) and in 11 control subjects (50.0%; $p < 0.005$). No adverse events were observed.

CONCLUSIONS: These preliminary results, obtained in a field-practice setting, indicates the effectiveness and safety of a well-standardized cranberry extract in the prevention of R-UTI.

Key Words:
Urinary tract infection, Cranberry, E. coli, Prevention.

Introduction

Lower urinary tract infections (UTIs) affect up to 50% of adult women, and are often due to *E. Coli*[1,2]. UTIs are also frequent in men and are often recurrent in subjects with anomalies of the lower urinary tract as well as in those suffering from partial or temporary block of the urinary catherization or afte surgery.

Recurrent UTI (R-UTI) has been defined as three episodes of UTI in one year or two episodes in over a six-month period. Recurrent UTIs represent a major source of morbidity and health care costs[3]. Long-term antibiotic prophylaxis reduces the frequency of R-UTIs in women[3]. However, long-term use of antiobiotics increases health costs and the risk of adverse effects, and may select adaptive, multi-drug resistant the efficacy of antimicrobial treatments and altering the intestinal flora. At present, there is no well-established recommendation for a 'standard' prophylactic antibiotic management to prevent the occurrence of R-UTI[3-5]. In addition, a number of signs and symptoms of UTIs may persist even in absence of a bacterial involvement or with a minimal, almost physiological bacterial concentration in the urines, since lower UTIs have a significant non-bacterial, inflammatory component[5,6].

Recently, cranberry extracts have been tested as a nutritional supplementation in the prevention of R-UTIs in subjects at risk, with mixed results[5,7-9]. However, evidence of efficacy should be considered only for well-characterized and reproducible products[8,9].

The proanthocyanidins (PACs) present in cranberries may inhibit P-fimbriated *E. coli* from ad-

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hering to uroepithelial cells[10,11]. P-fimbriae mediate adherence to uroepithelial cells by the activity of the P adhesin gene (*papG*). Moreover, dried cranberries and extracts[5,7] contain a high concentration of polyphenols that inhibit the adherence of bacteria to the mucosal and uro-epithelial cells in the lower uninary tract. Of note, the infecting bacteria may have a intestinal origin and the intestine tract could be an alternative site in which the active componentes of cranberry extract may interact with *E. coli* decreasing its infectivity[11]. Resveratrol, in cranberry extracts, decreases the pathogenicity of *Proteus mirabilis* by limiting urothelial cell invasion[12]. In addition, cranberry may improve the mucosal immunity to uropathogens[13,14].

Additional well-grounded evidence appears, however, necessary to better characterize the efficacy of cranberry extracts in the prevention of lower UTIs[8]. The aim of this pilot, registry study was to evaluate the prophylactic effects of oral supplementation with a new product (containing PACs in the range of 25.0-35.0%) reproducing the natural total profile of cranberry fruits in subjects with a previous history of recurrent UTI, over a 2-month follow-up.

Patients and Methods

Study design and subjects

This was a registry, supplement study (see[15] for a definition and a description of such studies). Subjects with a history of R-UTI (at least three symptomatic UTIs in the year before inclusion of two UTIs in the last six months) were eligible. Exclusion criteria were as follows: any chronic clinical condition or risk factors, immune-compromising diseases, concomitant infections of any nature, blood in the urines, antibiotic or corticosteroid treatment for any reason in the last 6 months, allergy of intollerance to cranberry.

Interventions

All patients received fosfomycin for one day. At day 5, an urinary colture was performed; if negative, the subject was suggested to take one capsule containing the new highly-standardized cranberry extract (Anthocran™) for 60 consecutive days. All subjects were also given lifestyle and hygiene advice (accurate washing, drinking and voiding at correct times, low caffeine, alchool and spice intake, moderate physical activity).

The registry recorded the occurrence of new UTI episodes over 2-month follow-up. A new episode was defined as follows: signs/symptoms of UTI, visible presence of blood and need for consultation and specialist's evaluation.

Statistical Analysis

Clinical effectiveness in the prevention of UTIs was determined according to three parameters: (i) comparison of the number of UTIs in the two months before the inclusion in the registry and during the registry period; (2) Number of symptom-free subjects during the registry period, duration of UTI episodes and need for medical attention; (3) normal urinalysis at the end of the registry period. All parameters were calculated for subjects on cranberry extracts and those who decided not to take this supplemention. Safety considerations were also performed.

All data were analyzed by descriptive statistics. On the basis of the model study by Burleigh et al[6], it was estimated that at more than 20 subjects per group would be needed to evaluate differences in the three target parameters between subjects on cranberry and those not on this supplementation after 60 days of Cranberry prophylaxis. Statistical differences were evaluated by the Student *t* test or the Mann-Whitney U-test, as necessary. A *p*-value <0.05 was considered statistically significant.

Results

In total, 22 patients completed the registry period in each of the two groups, for a total of 44 patients. Table I shows their baseline characteristics. The two groups were overall comparable for age and gender distribution, for the days of follow-up and also for the number of UTI episodes before inclusion. There were no drop-outs.

Table II shows the number of UTI episodes in single subjects. In the cranberry group, 75 UTI

Table I. Patients characteristics.

	Cranberry + Lifestyle advice (n=22)	Lifestyle advice only (n=22)
Females, number	16	17
Age, years (mean±SD)	39±4	39±3
Follow-up, days (mean±SD)	62±2	62±2

SD: standard deviation

episodes were reported in the two months before inclusion in the registry, compared with 20 episodes in the registry period: the reduction in the frequency of UTI episodes was 73.3% ($p < 0.05$). Conversely, this figure was 15.4% in the control group ($p < 0.05$), the difference between groups being statistical significant ($p = 0.012$).

Seven out of 22 (31.8%) subjects in the cranberry group were symptom-free during the registry period; no patient was symptom-free in the control group ($p < 0.05$). In addition, the mean duration of UTI episodes was 2.5±1.3 days in the cranberry group, compared with 3.6±1.7 days in subjects not on cranberry ($p < 0.05$). Three patients (13.6%) in the cranberry group and 8 (36.3%) in the control group required medical consultation for UTI symptoms ($p < 0.05$).

At the end of the registry, urine evaluation was completely negative for blood or bacteria in 20/22 subjects in the Cranberry group (90.9%) and in 11 control subjects (50.0%; $p < 0.005$).

No adverse events were observed in either group. Compliance to cranberry was optimal, with more than 95% of the doses correctly used.

Discussion

Lower UTIs are a common clinical entity which often does not arrive to the the attention of general practitioners or specialists, but is managed directly by subjects using over-the-counter products.

Among the over-the-counter products currently available, cranberry is particulary used, since a number of components in cranberry affect the evolution and physio-pathology of UTI and R-UTI. Importantly, the action of cranberry can minimize the inflammatory component of UTI, which cannot be effectively treated by antibiotic therapy. The results of the present registry study, conducted in a field-practice setting, add further evidence to the effectiveness and safety of cranberry extracts in the prevention of UTI in subjects with a history of R-UTIs. Subjects who added a well-standardized cranberry extract to lifestyle conselling had better clinical outcomes than those who only followed lifestyle advice. This advantage was observed in a number of parameters, including the number of UTI episodes, their duration, and the need for medical attention. Interestingly, also subjects who decided to follow advice only experienced a clinical benefit, as a confirmation of the importance of a correct lifestyle in the prevention of UTIs.

The need of a standardized and well-characterized extract reproducing the natural total profile of cranberry fruits is validated by a recent pharmacokinetic study which shows quantifiable phenolic acids and flavonoids in human urine after consuption of cranberry juice[16].

Conclusions

Given the overall limited number of subjects and the short follow-up of this registry study, its results are to be considered preliminary. Larger and controlled studies with a longer follow-up should be conducted also to investgate the potential effectiveness of the well-standardized cranberry extract used in this study in other settings (e.g. prostatitis, or pediatric subjects). While such studies appears awaited, available evidence seems to suggest that cranberry extract might have a role in the prevention of further lower UTIs episodes in subjects with an history of R-UTI.

Table II. Number of UTI episodes in single subjects.

	Cranberry + Lifestyle advice (n=22)		Lifestyle advice only (n=22)	
Subject number	*Before inclusion*	*Registry*	*Before inclusion*	*Registry*
1	4	2	3	3
2	3	0	3	2
3	4	1	3	3
4	3	2	4	2
5	4	1	3	3
6	4	1	4	4
7	3	0	4	4
8	3	0	3	2
9	4	1	4	3
10	3	0	4	3
11	3	1	5	3
12	5	1	4	4
13	3	0	4	3
14	2	0	3	3
15	3	0	4	3
16	4	1	3	4
17	4	2	3	3
18	3	1	3	2
19	3	2	4	3
20	3	1	4	2
21	4	2	3	3
22	3	1	3	4
Total	75	20	78	66

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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