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Cranberry Standardized Capsules May Prevent Recurrences of Urinary Tract Infections in Children

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Abstract

We conducted a prospective study with the aim to evaluate the efficacy and safety of standardized cranberry capsules as prophylaxis in children with recurrent Urinary Tract Infections (UTIs).

Therefore, children and adolescents, aged 2-18 years, with history of recurrent UTIs, were recruited for the study and randomized to receive cranberry in a standardized dose of cranberry extract 125 mg (proanthocyanidins 7.2%), vitamin C 7.5 mg and vitamin E 2.5 mg or not. They were followed for 1 year during which compliance, side-effects and UTI episodes were recorded.

Children on cranberry compared to control group presented significantly lower percentage of UTIs, fewer days/year on antibiotic treatment and lower percentage of initiation of antimicrobial prophylaxis ($p<0.05$) due to UTIs recurrences. In addition, in the subgroup of children with vesicoureteral reflux we observe a significant difference between the cranberry and the controls group in the number of UTIs ($p<0.05$). No side effects in cranberry group were reported. *Escherichia coli*, *Klebsiella* and *Proteus spp*. in this order were the predominant species isolated in both groups in the beginning and also in the end of the study. A trend of decrease of *E. coli* episodes in the cranberry group before and after the treatment was documented (83.3% *vs.* 66.6%), however, this was not significant ($p=0.28$).

It seems that the use of standardized dose of cranberry seems to be a secure and effective treatment for children with recurrent episodes of UTIs.

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Introduction

Urinary tract infections (UTIs) are very common during childhood. Furthermore, about 10% to 30% of children will experience a new UTI within the first year after the initial episode. Higher incidence of UTIs is observed in those children with vesicoureteral reflux, neurogenic bladder and congenital anomalies of the urinary tract [1,2]. In order to reduce the likelihood of UTI recurrence, antimicrobial prophylaxis is regarded as the treatment of choice for many years. However, the main disadvantage of long-term antimicrobial treatment is the development of resistant organisms [1,2]. Aiming to avoid prolonged antibiotic treatment, alternative prevention methods have been searched [3-5].

Cranberry (*Vaccinium macrocarpon*) seems to exert antiseptic and antimicrobial clinical effects in the urinary tract of humans through different mechanisms, some of them still under investigation. The first mechanism relies on its ability to acidify urine due to its high content of vitamin C, but mainly due to benzoic acid's antimicrobial action. Specifically, benzoic acid is excreted in urine as hippuric acid and the therapeutic effect of cranberry has long been attributed to hippuric acid which inhibits the growth of bacteria [6]. However, it has been shown that because of the low levels of benzoic acid in cranberry (<0.1%), a daily consumption of more than 4 liters of cranberry juice is required in order to acidify urine and achieve increased activity of hippuric acid [6,7]. Another protective mechanism against UTIs, which is considered the most important, is based on inhibition of bacterial adherence to the uroepithelium thus preventing colonization and infection [6,7]. Moreover, cranberry alone but also in combination with propolis seem to have a protective role against the virulence of uropathogenic *E. coli* species by changing the expression of specific genes involved in adhesion, motility, biofilm formation, iron metabolism and stress response [8].

Studies on the use of cranberry in the pediatric population are limited in number. However, researchers are shown an increasing interest for its use in this sensitive age. This trend is supported by the results obtained mainly in adults, the documented lack of side effects and the ease of administration as well as adequate patient compliance [9-11].

Table 1: Characteristics of study participants.

Characteristics	Cranberry* n=30 (%)	Controls* n=35(%)
Male/Female	23-Jul	26-Sep
Age (years)	7 ± 3.53	7.3 ± 3.54
History of UTIs (means, range)	3.3 (2–6)	3.1 (2–5)
History ≥ 3 UTIs	16 (53.3%)	17 (48.6%)
VUR, grade I,II	6 (20%)	8 (22.9%)
Neurogenic bladder	4 (13.3%)	6 (17.1%)
Antimicrobial prophylaxis before study	17 (56.7%)	20 (57.1%)

*There were no statistical significant differences in the characteristics between cranberry and controls group

UTI: Urinary Tract Infection; VUR: Vesicoureteral Reflux

The aim of our study was to evaluate the efficacy and safety of using cranberry as prophylaxis in children with recurrent UTIs.

Materials and Methods

Study subjects

This prospective study was conducted from June 2016 until May 2017. Children with history of recurrent UTIs, defined as 2 or more episodes of UTIs during the last 6 months, aged 2-14 years-old were assessed for eligibility. Children with mild neurogenic bladder dysfunction based on daytime storage symptoms such as urgency, urinary incontinence or holding maneuvers responding to conservative measures and without need of anticholinergic medication were also included. Exclusion criteria included vesicoureteral reflux ≥ grade III and other congenital anomalies of kidney and urinary tract, as leading causes of recurrent UTIs. The participants were randomized to receive standardized cranberry extract (capsules Mirtygil, Istituto Ganassini, SpA, Epsilon Health) or not.

Patients with positive urine culture (≥ 10^5 CFU/ml) of a pathogenic organism in midstream urine sample were considered to have UTI. Pediatric nephrologist assessed presence of urinary tract infection and systemic symptoms, in order to detect febrile UTI. Specific consultation was given to all children and parents regarding voiding and constipation problems. Urine analysis (U/A), urine culture (U/C) and patient examination was done monthly. In addition to our planned investigations, participants and their parents were educated to refer to our hospital when they showed symptoms that were suggestive of UTI. Asymptomatic patients occasionally faxed their U/A and U/C reports, but ill patients were referred to the hospital for performing more laboratory and imaging assessments. Parents kept a diary of daily treatment. Compliance, side-effects and results were recorded on regular follow-up visits every three months. Children were followed for at least one year. Our outcome measure was investigating the incidence of UTI in the cranberry and the controls group.

Cranberry formulation features

The cranberry formulation that was used was the commercially available cranberry capsules [MIRTYGIL®, Istituto Ganassini SpA (Di Ricerche Biochimiche, Milano, Italy) Epsilon Health]. Each capsule containing dry cranberry extract 125 mg (proanthocyanidins 7.2%), vitamin C 7.5 mg and vitamin E (mg a-TE) 2.5 mg. The dosage administered as prophylaxis was two capsules daily, taken once daily. Patients unable to swallow capsules received its contents diluted in liquid (milk, water, tea) or food (yogurt).

The study was conducted according to the Good Clinical Practice guidelines and the principles enunciated in the Declaration of Helsinki. All children's parents provided written informed consent before entering the study.

Statistical analysis

The results were analyzed by using the statistical program GraphPad Instat (Graphpad Inc, San Diego, CA) and descriptive statistics are presented as mean ± SD or median. Univariate analyses for group comparisons were performed using Mann-Whitney U, and dependent group comparisons were performed using Wilcoxon test. A p value of <0.05 indicated statistical significance.

Results and Discussion

A total of 76 children, 53 girls, were initially included in the study and 38/76 received cranberry. Eight out of 38 of the cranberry groups were excluded due to no compliance or loss of follow up and three controls were excluded due to loss of follow up. In the end, 30 children received cranberry for three months up to one year. Vesicoureteral reflux grade I and II presented 6/30 and 8/35 children of the cranberry and control group respectively (p>0.05). Mild neurogenic bladder symptoms had 4/30 and 6/35 children of the cranberry and control group respectively (p>0.05). Baseline characteristics of the patients included in the study were quite similar and are depicted in Table 1.

Five children (16.7%) in the cranberry group and 22 (62.8%) children in the control group had at least one recurrent UTI during the follow-up period. No child on cranberry extract presented 3 or more episodes of UTIs, while 4/22 (18%) children with recurrent UTIs in the control group presented ≥ 3episodes. Children on cranberry compared to controls group presented a significantly lower percentage of UTIs (p=0.0003), receiving cranberries for 178.2 ± 66.7 days. Moreover, children on cranberry regimen received antibiotic

Table 2: Outcome of study participants.

	Cranberry group n=30	Controls n=35	p
Patients with new UTI episode	5 (16.7%)	22 (62.8%)	3E-04
1 episode	4	11	
2 episodes	1	7	
3 episodes	-	3	
4 episodes	-	1	
UTIs in patients with VUR	1 (16.7%)	7 (87.5%)	0.026
UTIs in patients with mild neurogenic bladder dysfunction	2 (50%)	6 (100%)	0.13
Duration of antibiotic treatment (days/year)	10.4	16	0.002
Initiation of antimicrobial prophylaxis (%)	3.3	31.4	0.004

UTI: urinary tract infection, VUR: vesicoureteral reflux

Table 3: Pattern of pathogens before and after cranberry course of treatment.

Pathogens	Cranberry group	Controls
Before cranberry use (total episodes)	98	109
Escherichia coli (%)	83.7	78.9
Klebsiella species (%)	9.2	11
Proteus species (%)	4.1	3.7
Enterobacter species (%)	2	2.8
Pseudomonas species (%)	1	3.7
After cranberry use (total episodes)	6	38
Escherichia coli (%)	66.6	76.3
Klebsiella species (%)	16.7	13.2
Proteus species (%)	16.7	5.3
Enterobacter species (%)	0	2.6
Pseudomonas species (%)	0	2.6

treatment due to a UTI for notably fewer days per year (p=0.002). Furthermore, the percentage of children who initiated antimicrobial prophylaxis on account of UTI recurrences during the follow-up period was significantly lower in the cranberry group (p=0.004) (Table 2). Although the sample size of patients with vesicoureteral reflux was small we observe a significant difference between the cranberry and the controls group in the number of UTIs (16.7% *vs.* 87.5%, *p*=0.026) with days without UTI being between the two groups being 204 ± 62 and 159 ± 52 days, respectively. It should be noted that no side effects have been reported from the cranberry recipients.

The pattern of pathogens is described in Table 3. *E. coli*, *Klebsiella* and *Proteus* spp., in this order, were the predominant species isolated in both groups, in the beginning and also in the end of the study, with no statistical difference between the two groups. A trend of decrease of *E. coli* episodes in the cranberry group before and after the treatment was documented (83.3% *vs.* 66.6%), however, this was not significant (p=0.28).

According to the results of the present study, receiving standardized cranberry capsules on a daily basis reduced the number of children experiencing UTI recurrences as well as the number of UTI recurrent episodes.

Cochrane Database Systematic Review of 2012 that included 24 studies with o total of 4473 participants showed that cranberry products had not reduced UTIs compared with placebo, water or no treatment. Also in the same study authors have underlined the need cranberry preparation to be quantified for the active ingredient, before being evaluated in a study [12]. Studies on the use of cranberry in the pediatric population are limited in number. Regarding children with history of UTIs in a randomized study from Italy has been shown a significant reduction in the risk of repeated UTIs in the cranberry group compared with the *Lactobacillus* GG group and the control group, suggesting a protective effect of cranberry juice [13]. Salo et al. [14] in a double-blind randomized multicenter study found no differences in timing between first recurrences of UTI. However, in accordance with our study, children in the cranberry group had significantly fewer days on antimicrobials and lower incidence density per child/year of UTIs. Moreover in a systematic review, has been reported that cranberries reduced the risk ratio for UTIs in all population groups with greater prophylactic effect in sub-group of patients at risk for UTIs of any cause [15]. In agreement with our results but in an older group of population, that of young adolescents aged 12-18 years of age with recurrent UTIs, the prophylactic effect of standardized cranberry extract has also been demonstrated by Ledda A et al. [16]. However, in the above mentioned study, a highly standardized cranberry extract has been used of 36 mg proanthocyanidins compared to our cranberry treatment of 19 mg proanthocyanidins once daily. As dietary supplements of cranberries extracts may contain different ingredients and do not require extensive pre-marketing approval from the U.S. Food and Drug Administration, it is very important studies to mention the specific product that has been used to certify its safety or effectiveness. Wan et al. [17] have reported that in uncircumcised boys cranberries may prevent UTIs and this beneficial effect was even higher of the circumcision for circumcised boys. In this study, cranberry group drank specific dose of highly concentrated cranberry juice, suggesting that even standardized juice consumption may have a beneficial effect on UTIs. Moreover, cranberry extract enriched with proanthocyanidins or propolis may be even more effective [8,18].

Neurogenic bladder with mild symptoms is common in children. Foda et al. and Schlager et al. [19,20] found no beneficial effect of concentrated cranberry juice in children with neurogenic bladder and UTIs. However, in a randomized controlled prospective trial which used daily cranberry capsules in children with neurogenic bladder caused by myelomeningocele, a decrease in UTIs has been reported [21]. The small number of children with neurogenic bladder did not allow us to observe significant differences between the groups. Moreover, our population presented only mild neurogenic bladder symptoms, without any underlying serious problem or need for pharmaceutical treatment or catheterization and the results is difficult to be discussed with other studies which included patients with profoundly neurogenic bladder dysfunction. Currently, for children with neurogenic bladder, no prophylactic measure with evidence-based efficacy exists [22].

There are only limited data regarding efficacy of cranberry administration in children with vesicoureteral reflux. Nishizaki N et al. [23] reported that cranberry juice is comparable to cefaclor as prophylaxis for the prevention of recurrent UTIs in children with different grades of VUR and proposed cranberry juice as an alternative choice for antibiotic prophylaxis in this subgroup of children. However, recent studies have demonstrated that compared to no treatment, continuous antibiotic prophylaxis significantly reduced the risk of febrile and symptomatic urinary tract infections in children with vesicoureteral reflux grade ≥ 3, although it increased the risk of infection due to antibiotic resistant [24,25]. As the grade of reflux is a major factor for recurrent UTIs we use cranberry extract only in children with VUR below grade III. In this subgroup of children, we observed a significant difference between the cranberry group and the control group in the reduction of the number of UTIs. However, the sample size was small so we cannot draw any reliable and definitive conclusions from that.

Concerning the effectiveness of cranberry versus antibiotic prophylaxis for recurrent UTIs, there are limited data. Cranberry juice has been compared to low dose of trimethoprime in terms of preventing recurrent UTIs and the effectiveness of all treatments were comparable [26]. In our study a significantly lower percentage of children in the cranberry group compared to controls initiated antimicrobial prophylaxis on account of UTI recurrences during the follow-up period.

The number of subjects in the current study was small and

limitations imposed by the data may affect the ability to draw definite conclusions. In addition, this is not a double-blind placebo-control study, so further limitations are arise. Therefore, there were no recommendations for the use of cranberries in children but the potential of cranberry products to act as a non-antibiotic alternative for preventing UTI seems to be obvious.

Conclusion

The use of standardized low dose of cranberry extract was effective in reducing the number of children who experienced a UTI recurrence, the actual number of recurrences and related antimicrobial use, suggesting that cranberry is an effective prophylaxis treatment for children with UTI recurrent episodes. The specific cranberry extract was well tolerated by all children, even the younger ones, with no side effects mentioned. Taking into account the need to decrease the use of antibiotics at least as prophylaxis in pediatric population at risk for UTIs, we propose standardized cranberry extract as an effective and secure measure in the subgroup of pediatric population with recurrent UTIs and without evidence based guidelines for antibiotic prophylaxis.

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