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A SINGLE BLIND, RANDOMIZED CONTROLLED TRIAL ON THE EFFECT OF CRANBERRY JUICE AS ADJUNCT TO ANTIBIOTICS IN THE TREATMENT OF RECURRENT URINARY TRACT INFECTION IN CHILDREN

MA. CECILIA D. ALINEA, MD*, JACINTO BLAS V. MANTARING III, MD*

Abstract

Objectives. **The main objective of this study is to determine the effect of cranberry juice as adjunct to antibiotics in the rate of change in pyuria and bacteriuria in children with recurrent urinary tract infection (UTI) secondary to anatomic and/or functional genitourinary abnormalities after 4 weeks of intake. A sociodemographic profile of these children were also determined as well as the changes in duration of symptoms manifested after 4 weeks of the study.**

Methodology.

Design. **A single blind, randomized controlled trial was used in this study.**

Setting. **Utilized in this study were children who sought consult at the Out Patient Department (OPD) Sick Child, Renal and Urology Clinics of the Philippine General Hospital.**

Participants. **Fifty (50) children, with an age range of 2-11 years, and with anatomic and/or functional genitourinary problems were included in the study.**

Main Outcome Measures. **The rate of change in pyuria (pus cells or WBC count in urine) and bacteriuria (number of colony forming units in urine culture) were the main outcome measures used in the study.**

Results. **Neurogenic bladder of various etiology was the most common genitourinary abnormality, followed by vesicoureteral reflux. Among the usual manifestations of UTI noted were dysuria, fever, frequency and hypogastric pain. *Escherichia coli (E. coli)* was still the most common organism found in bacterial cultures, followed by *Klebsiella, Enterobacter and Pseudomonas.* Cotrimoxazole was the most common medication used in prophylactic treatment. Pus cell or White Blood Cell count (WBC in urine) was significantly different at baseline in the two groups, but a general trend of decreasing count was noted up to week 4 of both treatment groups. This decrease, though, was not significant. Significant decrease in the number of colony forming units (CFU) was noted at baseline, week 2 and week 3 of the control group. The rate of change in the CFUs between groups, however, is not significant. Clinical manifestations such as dysuria, frequency, fever, hypogastric pain and vomiting improved after 4 weeks of intake of cranberry juice.**

Conclusion. **In conclusion, no significant change was noted between the cranberry and the control group in terms of biochemical parameters, but improvement in symptomatology of UTI in the cranberry juice may suggest a promising outcome for this juice in terms of clinical manifestations.**

Recommendations. **Recommendations for further studies include the use of double blinding in randomized controlled trials, and possibly a larger population. Since the definite amount and period of intake of cranberry juice to effect a significant decrease in bacteriuria yet to be determined, study designs should answer this particular issue. Further investigation on possible side effects should also be looked into.**

INTRODUCTION

The urinary tract is a common site for bacterial infections in children. In the pediatric population, its epidemiology is clouded by the variability and non-specificity of signs of infection in infants and young children. It has been estimated that approximately 2% of boys and 9% of girls will experience a symptomatic urinary tract infection (UTI) for at least one episode by the age of 7 years[1]. It occurs more commonly in boys up to the age of 6-12 months, but overall occurs about three times more often in girls (1-3% in boys, 3-7% in girls)[2]. Death is now a rare complication but hospitalization is frequently required (40%), particularly in infancy[3]. Approximately 40% of children affected develop transient damage to the kidneys[3]. Permanent damage occurs in about 5%, sometimes even following a singe infection[4].

Children who have had one infection are at risk of further infections. Recurrent urinary tract infection occurs in up to 30% of children[2]. Risk factors for recurrent infection are the presence of genitourinary abnormalities, previous infections and bladder instability[5]. Recurrence of urinary tract infection are more common in girls than in boys[6].

Faced with the risk of pyelonephritis-induced permanent kidney damage and the unpleasant acute illness caused by urinary tract infection, long-term or prophylactic antibiotic treatment is given to these children, with the aim of preventing recurrence. Usual

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* University of the Philippines, College of Medicine-Philippine General Hospital

medications used include cotrimoxazole, nitrofurantoin and trimethoprin. These drugs may cause side effects and promote the development of resistant bacteria. Alternatives to pharmacologic agents with less side effects (eg. Herbal plants, fruits, and the like) may be more beneficial to these children than long-term antibiotic therapy.

According to folk wisdom, cranberry juice can be used to prevent the occurrence of urinary tract infection. As early as 1914, there have been reports of its efficacy with regards to this disease[7]. Blatherwick reported that cranberries are particularly rich in benzoic acid, excreted as hippuric acid in the urine. Studies from the 1920's to the 1970's suggested a bacteriostatic effect, but other studies have yielded conflicting results concerning urinary acidification[8].

Cranberries contain quinic acid, malic acid and citric acid as well as glucose and fructose. Recently, it has been suggested that quinic acid causes large amounts of hippuric acid to be excreted in the urine which acts as an antibacterial agent[9], though some studies have shown no difference in the levels or only a transient effect[10]. More recent studies have shown that cranberries prevent the adhesion of *Escherichia coli (E. coli)*, the most common bacteria causing urinary tract infection, to cells of the urinary and alimentary tract. Aronson, et al have reported that there are compounds that block the adherence of bacteria to the mucosal cells of the urinary bladder of mice which prevent the development of urinary tract infection. Uropathogenic *E. coli* adhere to these cells because they have adhesins (designated MS and MR) on the hair-like fimbriae (or pili) that protrude from their surfaces[11]. Studies done in cell culture by Sobota[12] and Schmidt and Sobota[13] show that cranberry juice might act to reduce UTI by the same mechanism.

A study done by Avorn, et al, in 1994, found that regular consumption of cranberry juice cocktail significantly reduced the bacteria association with urinary tract infections among elderly women (average age of 78 years). While it had been long suspected that there was a connection between cranberry juice and urinary tract health, this study provided the clinical evidence to document this claim. This study concluded that there was something specific to the cranberry that prevented bacteria from adhering to the lining of the bladder.[14]

Cranberry juice contains two compounds that inhibit the *E. coli* adhesins. One is fructose, a constituent of all fruit juices. This inhibits the MS fimbrial adhesin. The other inhibitor is recently identified in 1998 (Rutgers University) to be condensed tannins, also known as proanthocyanidins. Through a bioassay-directed fractionation process, this compound was eventually isolated after many years, and was the one responsible for inhibiting the MR adhesins associated with the pylonephritogenic strains of *E. coli*. Howell estimates that the amount of condensed tannins in a 10-ounce glass of cranberry juice cocktail consumed on a daily basis would help prevent *E. coli* from attaching to the walls of the bladder and kidney and ward off UTI[15].

Other juices have been studied to determine whether they contain the high molecular weight inhibitor, by determining their ability to inhibit hemagglutination caused by urinary and non-urinary isolates of *E. coli* expressing MR adhesins. Of the seven juices (blueberry, cranberry, grapefruit, guava, mango, orange and pineapple), only those from the plants of the Vaccinium genus (family Ericacaea), that is, blueberry and cranberry, contained this inhibitor[16].

Cranberries (*Vaccinium macrocarpon)* are of three native North American fruits. They have an appealing red color and astringent taste. They are processed into three basic categories: fresh (5%), sauce product concentrate and various applications (35%), and juice drinks/cocktails (10%). In the United States, the cocktail juice form has been noted to be palatable to children's taste buds. With the knowledge of what it can offer those with urinary tract infection, it may be a promising adjunct or even alternative to long-term antibiotic use which eventually produces side effects. It was seemingly beneficial contents may even allow for a shorter duration of antibiotic use.

It is, thus, the main objective of this study to determine if cranberry juice as an adjunct to antibiotics will lead to earlier improvement in pyuria and bacteriuria than antibiotics with a control, in pediatric patients diagnosed with recurrent urinary tract infection (UTI).

Specific objectives include:

1. To determine the baseline sociodemographic data and clinical profile of the subjects
2. To determine if administration of antibiotics with cranberry juice can achieve a greater mean reduction in pyuria as compared to antibiotics and a control at the end of 4 weeks.
3. To determine if administration of antibiotics with cranberry juice can achieve a greater mean reduction (less than 100,000 colonies) in bacteriuria

compared to administering antibiotics and a control at the end of 4 weeks.

4. To determine if administration of cranberry juice plus antibiotics decrease the duration of symptoms earlier than antibiotics plus control.
5. To identify possible side effects of cranberry juice.

RESEARCH QUESTION

Among pediatric patients diagnosed with recurrent urinary tract infection consulting in a tertiary government hospital, what is the effect of cranberry juice as adjunct to antibiotics in bringing about an earlier and faster reduction in pyuria and bacteriuria as compared to antibiotics alone?

MATERIALS AND METHODS

A single blind, prospective randomized controlled trial was utilized in this study.

Subjects included male and female children aged 1 to 17 years consulting in a tertiary hospital's Out Patient Department (OPD), or admitted at the Surgical or Rehabilitation Wards (Wards 2,4,5,6), with anatomic and/or functional problems involving the urinary tract and diagnosed to have recurrent UTI by the number of recurrences of the disease (at least twice a year), symptoms (fever, dysuria, frequency, vomiting, lethargy, etc.), supported by a urinalysis (catheterized) showing pyuria (WBC>5/hpf) and bacteriuria (>100,000 colonies of bacteria) by culture. Antibiotics may or may not have been taken prior to onset of study. Voluntary, written consent had been secured for all those included in the study. Excluded were those who have intake of similar juices which may have similar effect as cranberry juice (eg. Noni juice, blueberry juice, etc.).

Assuming a power of 80%, with the smallest significant difference of 0.8, and a probability of a type 1 error of 0.05, this study required a sample size of 25 subjects per group.

All eligible subjects have been randomly assigned into 2 groups using an odd-even number scheme. Numbers 1-50 were contained in individually sealed envelopes and the guardian of the subject randomly selected one from the 50 envelopes. Odd numbers were given treatment (A) antibiotics and a control and Even numbers were given treatment (B) antibiotics and cranberry juice. After the assignment of treatment group, the investigator obtained a complete medical history and physical examination and instructed the primary caretaker of the subjects in the proper method of obtaining a catheterized urine specimen.

Treatment A received antibiotics plus a control (Sunkist Grape Juice), dispensed in 7 containers with secure lids, prepared by the investigator. Each container contained 300 ml of the juice which the child drank daily (300 ml/day) for 4 weeks. Treatment B, consisting of antibiotics plus cranberry juice cocktail (Ocean Spray Cranberry Juice Cocktail, Lakesville, Massachusettes), were also dispensed in sealed containers, each container also containing 300 ml of the cocktail. Subjects belonging to this treatment group also took 300 ml/day of cranberry juice daily for 4 weeks. Children and their guardians were instructed not to consume any other cranberry, blueberry or other similar products during the study period except the cranberry juice being given by the investigator. A form-cum-checklist containing the date, amount and person who gave the juice was given to all the guardians of the subjects weekly, to be surrendered during the next visit to monitor compliance to the regimen.

Standard urinalysis, bacterial culture, and antibiotic testing were performed on each urine sample immediately after collection every week for 4 weeks. Samples were sent to the Microscopy (for urinalysis) and Microbiology (bacterial culture) sections of the Department of Laboratories of the Philippine General Hospital. Only one medical technologist at the Microscopy Lab and one from the Microbiology unit read the results. Once culture and sensitivity have been determined, the initial drug was either retained or discontinued and replaced by a more sensitive drug. If the child was already on prophylactic antibiotics, this drug was continued.

Each child was seen weekly by the investigator either during her Continuity Clinic at the OPD on Tuesdays or on Saturdays (Wards 9 or 11). During the weekly visit, a juice container count was performed and the form-cum-checklist was collected to assess compliance. Symptoms of urinary tract infection and all medications were recorded as well as perceived side effects. Proper collection of urine for the above tests were also done at this time.

Drop-outs were analyzed using an "intention-to-treat" analysis.

The primary outcome variables of this study were the rates of reduction of pyuria and bacteriuria across time and between groups. Secondary outcomes include rate of change in symptoms referrable to urinary tract infection and the presence or absence of side effects.

A 95% confidence interval was used in this study. Data was analyzed using the software SPSS. Measures of central tendencies (mean, standard deviation), frequencies and ANOVA were computed to determine for any significance difference between genders. Paired T-test was used to determine if there was a significant difference on pyuria and bacteriuria between groups. Test of proportions using the software STATISTICA was used to determine if there was a significant difference on symptoms between groups.

RESULTS

Baseline characteristics of the subjects involved in the study showed an age range of 2 to 11 years for both treatment groups (Cranberry group (CR)=6.96 +/ - 4.82; Control group (CO)= 7.16 +/- 4.47), majority of whom were females. No significant difference was noted between genders (p = 0.565). Genitourinary abnormalities were noted in 76% of the Cranberry group and 92% in the Control group (p value=0.5005). Majority of these abnormalities include: neurogenic bladder of various etiology , vesicoureteral reflux and hydronephrosis. (Table 1)

The most common symptoms referrable to urinary tract infection were dysuria, fever, frequency of urination, and hypogastric pain. Among the symptoms, hematuria, abdominal distention, poor feeding and lethargy were found to be significant between the 2 groups. (Table 1)

The organism most commonly isolated were: *E.coli, Klebsiella spp, Enterobacter spp* and *Pseudomonas spp.* All subjects were receiving prophylactic treatment during time of study and the drug most commonly used was cotrimoxazole (CR= 80%, CO= 68%) at 2 mg/kg/dose once a day. Other medications used were cefuroxime, amoxicillin-clavulanic acid (co-amoxiclav) and amoxicillin. (Table 1)

Table 1. Baseline measurement of study participants

	CRANBERRY GROUP	CONTROL GROUP	P VALUE
Number of participants	25	25	
Mean +/- SD age (years)	6. 96 +/ 4.82	7. 16 +/- 4. 47	
Gender (%) Male Female	 1. (40) 15 (60)	 8 (32) 17 (68)	0.565
History of genitourinary anatomic abnormality (%) Yes No	 19 (76) 6 (24)	 23 (92) 2 (8)	
Genitourinary abnormalities noted: •Hydronephrosis •Neurogenic bladder 2 to: Lipomyelomeningocoele S/P repair Lumbosacral meningocoele No repair S/P repair Neurodegenerative disease Spina Bifida Transverse myelitis Vesicoureteral reflux •Penile agenesis, S/P urethrostomy •Renal agenesis •Ureterocoele •Vesicoureteral reflux (VUR) •VUR with hydronephrosis	 4 (16) wlr 1.(8) 4 (16) 1.(4) 2.(4) • (4) • (4) 1.(4) 6 (24)	 • (8) • (4) 3 (12) 3 (12) • (8) • (4) • (8) 1.(32) 1 (4)	
Genitourinary functional abnormalities: •Cystitis •Cystolithiasis •Nephrocalcinosis •Urethritis •Vulvovaginitis	1.(4) • (4) 1.(4) 1 2w (4)	1 (4)	

Table 1. Baseline measurement of study participants *(cont...)*

	CRANBERRY GROUP	CONTROL GROUP	P VALUE
Symptoms referrable to UTI at baseline:			
•Abdominal distention	•(8)	1.(24)	0.0009*
•Dysuria	1.(92)	25 (100)	0.7678
•Fever	• (84)	20 (80)	0.8660
•Frequency	• (72)	18 (72)	1.0000
•Hematuria	2 (8)	4 (16)	0.0223*
•Poor feeding	12 (48)	1. (28)	0.0000*
•Hypogastric pain	2 (8)	• (68)	0.2298
•Lethargy	3 (12)	• (24)	0.0009*
•Vomiting		5 (20)	0.0835*
Medications, # patients with intake (%)			
•Cotrimoxazole	• (80)	• (68)	
•Cefuroxime	1.(8)	1.(24)	
•Co-amoxyclav	2.(8)	2.(4)	
•Macrodantin	•f (4)	1 (4)	
•Amoxicillin			
Bacteriuria (>100,000 CFU) with pyuria at baseline, # patients with (%)	23 (92)	24 (96)	
Organisms isolated at baseline, # patients with (%)			
•Acinetobacter	1 (4)	1(4)	
•Enterobacter spp.	3 (12)	• (52)	
•Enterococcus	2 (8)	1.(28)	
•E. coli	• (40)	• (12)	
•Gram negative organisms	1.(8)	1(4)	
•Klebsiella spp.	3 (12)		
•S. epidermidis	• (8)		
•Pseudomonas spp.	2 (8)		
•None			

Baseline count of pus cells (WBC) in the placebo group was significantly different (p value= 0.013) from that of the Cranberry group. Comparing the rate of change in WBC count, there was no significant decrease noted in the 2 groups across time (Figure 1) though there was a decreasing trend from week 2 to 4 in the cranberry group.

Baseline number of Colony Forming Units (CFU) was comparable between the two groups. Comparing the rate of change in CFU, there was no significant decrease in both groups across time, though there was a general decreasing trend observed (Figure 2).

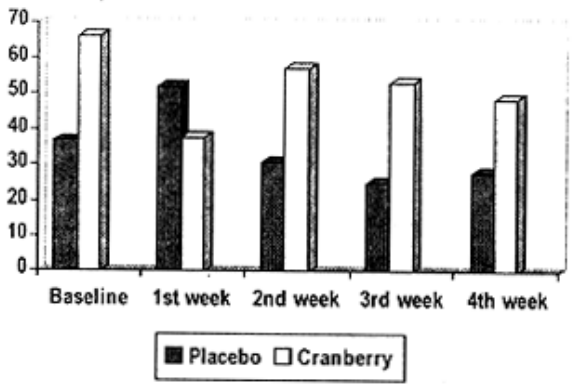

Figure 1. Rate of change in WBC coun between the 2 groups across time.

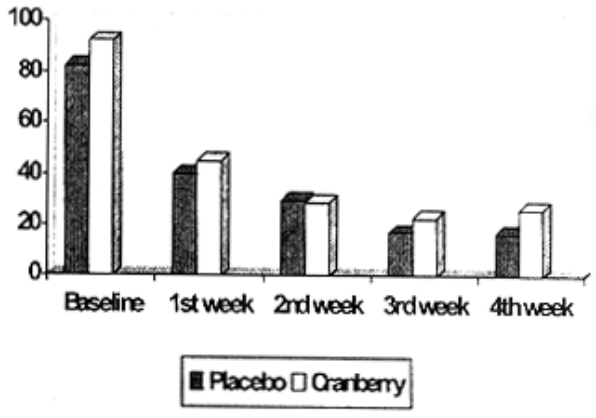

Figure 2. Rate of change in CFU's between the 2 groups across time

After 4 weeks, the number of patients suffering from practically all the symptoms gathered such as dysuria, hematuria, abdominal distention, frequency, fever, hypogastric pain, lethargy, and vomiting, and hypogastric pain were significantly reduced in the cranberry group compared to those in the placebo group (Figures 3 and 4).

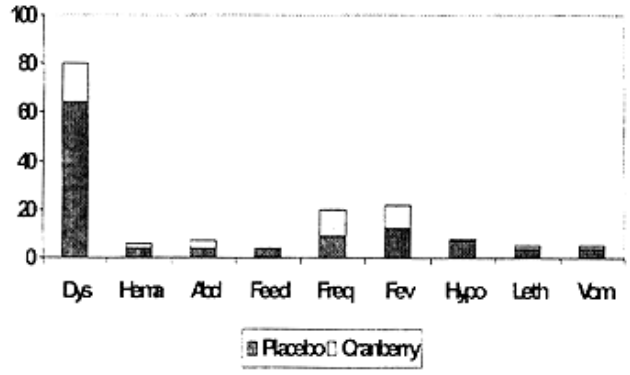

Figure 3. Number of patients suffering from different symptoms on baseline

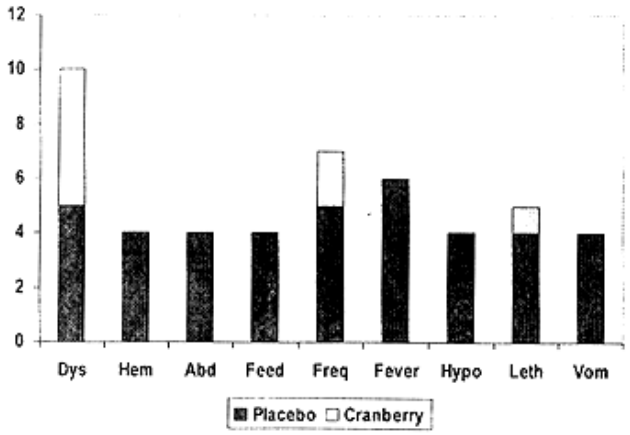

Figure 4. Number of patients suffering from different symptoms after 4 weeks.

Four subjects, all belonging to the cranberry group, complained of constipation (4%), diarrhea (8%), and stomach pain (4%). All these complaints were also reported to disappear within the time that the juice was still being taken. Symptoms were reported to disappear within the first two weeks of intake of the juice. (Table 7)

Table 2. Observed side effects of both groups

SIDE EFFECTS (%)	CRANBERRY GROUP	PLACEBO GROUP
Constipation	1 (4)	0
Diarrhea	2 (8)	0
Stomach pain	1 (4)	0

DISCUSSION

The Cochrane Renal Group has performed a thorough search among all randomized or quasi-randomized controlled trials of cranberry juice or cranberry products for the treatment of urinary tract infections among men, women and children, and concluded that no randomized trial assessing the effectiveness of the juice was found[17]. Despite this, there were still on-going trials advocating the hypothesis that cranberry juice and its other products may bring about improvement in patients with urinary tract infection. Since there were still a few studies performed in children, the present study was done to see if it could bring about this desired outcome in the pediatric age group, keeping the faith that the cranberry fruit's components well-known to prevent adhesion of bacteria to uroepithelial cells hold true.

The present study's outcome showed that there was no significant difference between the cranberry and control groups in terms of decrease in pyuria (as seen in pus cell count or WBC) and bacteriuria (as seen in the number of colony forming units or CFU). This implies that the control drink has the same effect as that of cranberry juice in achieving the result of decreasing pyuria and bacteriuria. Variables such as bladder wash-out and compliance to the regimen should be taken into consideration in this matter. A child who may be drinking more fluids than the required 300 ml in the study will facilitate a shorter duration of time for bacteria along the uroepithelial lining to spend in the urinary tract. Taking in less volume or incorrect frequency of intake of cranberry juice by participants may have preempted the supposed effects of the juice as measured biochemically.

Several reasons may be considered for arriving at this outcome. One was that at baseline, a number of sociodemographic characteristics were not comparable between groups. Although age and gender (p value= 0.565) were comparable, the number of participants with a history of genitourinary anatomic abnormalities was bigger in the control group compared to that of the cranberry group. In terms of the clinical manifestations, more participants were included in the control group in symptoms such as hematuria, abdominal distention, poor feeding, and lethargy, thus showing significantly different results.

A number of important factors may have contributed to an incomparable baseline data in this study. One is that the study design used, single blinded randomized controlled trial, may not have been designed

properly to prevent bias. Randomization, if well designed and implemented, should adequately prevent biases not inherent to the participants not to the study itself. In this study, only the participants were blinded to the treatment being given to them, not the investigator. This may have ushered a bias towards the cranberry group since the study would want to see if cranberry juice was more effective than the control drink. Another contributory factor was the presence of drop-outs in the control group. Four participants from this group failed to follow-up on the 2nd-3rd week of intervention, thus were treated as "worst case scenarios", with no decrease in WBC and CFU for 4 weeks. Inadequate sample size may also play a role.

Although a definite amount and duration of intake of cranberry juice were specified by researchers at Rutgers University in 1998 upon their discovery of proanthocyanidins[13], other studies claim otherwise. Thus, a universally accepted amount and duration of intake were yet to be established. The amount and duration used in this present study may be inadequate.

In 1999, Schlager, et al did a study on the effect of cranberry juice on bacteriuria in children with neurogenic bladder (NB) receiving clean intermittent catheterization (CIC). To determine the effect of the juice on the rates of bacteriuria and symptomatic urinary tract infection, a double-blind, placebo-controlled cross-over study of 15 children with NB secondary to myelomeningocoele were given cranberry concentrate for 3 months then a placebo concentrate for the next 3 months. The authors concluded that the cranberry concentrate had no effect on bacteriuria in this population[18]. This may support the present findings of the study.

Subjects with dysuria, frequency, fever, vomiting, and hypogastric pain significantly decreased in number in the cranberry group. After the first week of intake of the juice, children with vomiting and hypogastric pain have been noted to decrease in number already (Table 6). This may mean that though the biochemical parameters did not show any significant difference, the clinical parameters showed otherwise. Subjects with symptoms usually associated with urinary tract infection in children such as fever, vomiting, hypogastric pain and frequency (in older children) were noted to be significantly different from the control group. In children, the relief of symptoms is very important in managing this disease. Cranberry juice may hold promise in terms of this aspect of treatment in UTI.

A handful of children in the cranberry group reported experiencing constipation, diarrhea and stomach pain early on in the study, but these complaints dissipated after the 2nd week of taking the regimen. Though studies have shown that cranberry juice has minimal or no side effect at all, further investigations should be performed regarding this aspect.

Recommendations for further studies include the use of double blinding in randomized controlled trials, and possibly a larger population. Since the definite amount and period of intake of cranberry juice to effect a significant decrease in bacteriuria are yet to be determined, study designs should answer this particular issue. Further investigation on possible side effects should also be looked into.

CONCLUSION

Urinary tract infection (UTI) in children is not as uncommon as many people think. With at least one episode of UTI, they were at risk of having further infections, specially recurrent UTI. Antibiotics were the mainstay treatment of this disease but with the possible side effects they bring, alternatives to such treatment have increased in popularity, one of which is the use of cranberry juice. This study explored the effect of cranberry juice as adjunct to antibiotics in the treatment of recurrent UTI in children. The study population was composed of diagnosed recurrent UTI patients with an age range of 2-11 years of age, majority of whom were females. A large number of participants had genitourinary anatomic and functional abnormalities, the most common of which was vesicoureteral reflux and neurogenic bladder of various etiology. The most commonly encountered symptoms at baseline are frequency, dysuria, hypogastric pain and fever. Cotrimoxazole was the most frequently used drug, usually as prophylactic treatment. Majority of the participants have colony forming units (CFU) in their urine culture of >100,000, with *Escherichia coli (E. coli)* as the most common organism.

There was no significant difference in the rate of reduction of WBC and CFU between cranberry and the control groups, but a decreasing trend was noted across time (4 weeks). Though results were not significant in the biochemical parameters, a significant decrease in the number of children with fever, vomiting, hypogastric pain and frequency were noted in the cranberry group. This may indicate a promising role for cranberry juice in decreasing discomfort among symptomatic children.

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