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Original Research Article

A study to evaluate the efficacy of cranberry extract supplements in prevention of recurrent urinary tract infections in female patients

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ABSTRACT

Background: Recurrence of urinary tract infections (UTI) are either due to re infection or relapse. Overall likelihood of developing UTI is approximately 30 times higher in women than men due to their anatomical peculiarities. The objective was to evaluate efficacy of cranberry extract supplementations in prevention of recurrent UTI in female patients, assess the quality of life of patients, medication adherence of patients and effect of patient counselling.

Methods: A prospective observational study was carried out for a period of 6 months and samples were taken from the Urology Department of Cosmopolitan Hospital, Trivandrum, Kerala. The selected patients were administered with cranberry extract supplements after their regular Antibiotic therapy and were observed for recurrence for a period of six months. Three follow ups were taken and the betterment was assessed using the score from prepared proforma.

Results: 84 patients were analysed and among them we observed and concluded that 86.9% of patients were free of recurrent infection. Study shows that *E. coli* was the commonest infectious organism causing UTI. In this study the most commonly observed symptom of UTI was lower abdominal pain and the most common co morbidity was DM.

Conclusions: Through this study it was concluded that the cranberry extract supplements significantly reduced the recurrence of UTI in women. Since the antibiotic prophylaxis is having the risk of developing resistance and side effects, the cranberry extract supplements can be suggested as a best alternative to antibiotics in recurrent UTI prophylaxis.

Keywords: Cranberry, *E. coli*, Recurrent infections, Symptoms, Urine routine examination, UTI

INTRODUCTION

Urinary tract infections are one of the leading cause of gram negative bacteraemia for patients of all ages. The infection of the bladder and urethra are referred to as the infection of the lower urinary tract whereas the kidney and ureter infection is an indication of upper urinary tract infection.¹ UTI can be asymptomatic or symptomatic characterized by a wide spectrum of symptoms ranging from mild burning micturition to bacteraemia, sepsis or even death.² Other complications caused by UTI's are bladder infection (cystitis), urethral infection (urethritis),

kidney infection (pyelonephritis) and infection of the ureter (ureteritis). UTIs can be classified as uncomplicated or complicated (based on the factor that triggers the infection or primary or recurrent (depending on the nature of occurrence).^{3,4} Recurrent UTIs are common in women and are associated with considerable morbidity and health care use. The clinical features, diagnostic tests and causative organisms are often similar to those of single cases of UTI although there are additional treatment strategies and prevention measures to consider with recurrent UTI.^{5,6}

Recurrent UTI's include relapses (symptomatic recurrent UTI'S with the same organism following adequate therapy) and re infection (recurrent UTIs with previously isolated bacteria after treatment and with a negative intervening urine culture for a recurrent UTI caused by a second bacterial isolate).⁷ Most recurrent UTIs are thought to be caused by re infection with same organism. Recurrent UTI in adult women is usually treated with long term low dose antibiotics and current national and international guideline recommend this as the "gold standard" preventive treatment.⁸⁻¹⁰ Although they are reasonably effective long term antibiotics can result in developing resistance in bacteria. This has lead clinicians and patients alike to explore potential non antibiotic option for recurrent UTI prevention.¹¹ Cranberries have been used widely for several decades for the prevention and treatment of UTI. No definite mechanism of action has been established in the prevention of UTI however the main suggestion is that cranberries prevent bacteria from adhering to uro epithelial cells that line the bladder wall.¹²⁻¹⁵

So in this study we have evaluated efficacy of cranberry extract supplementations in prevention of recurrent UTI in female patients; and assessing the medication adherence of patients.

METHODS

It was an observational study carried out for a period of 6 months (December 2018-May 2019) on outpatients and inpatients from the Department of Urology, General Medicine, Gynaecology and General Surgery at cosmopolitan hospital were included during the study period.

Sample size

Minimum sample size required in the present study was 80.

Inclusion criteria

Females patients of age between 18-70 who are willing to participate in the study, patients with clinically reported UTI, patient with lifestyle diseases such as DM, HTN and other comorbidities and patients with history of recurrent UTI were chosen in our study.

Exclusion criteria

Post catheterised patients, patients with any chronic illness or risk factors, allergy or intolerance to cranberry, immuno compromised patients, pregnant women and patients not willing to participate in study.

Data collection

A written informed consent will be taken in prescribed format from the female patients diagnosed with urinary

tract infection. All information relevant to the study will be collected from the medical records. The demographic characters, clinical features and other details will be documented in the proforma. The other data collection tools include EQ 5D 5L, MGL and KAP questionnaires.

Study procedure

Female patients presenting with UTI are selected from various departments (Urology, General medicine, Gynaecology, General surgery) of the Hospital. Patients satisfying the inclusion and exclusion criteria and who were willing to participate in the study are included after obtaining their informed consent. Patients were provided with the proforma to get details about their clinical symptom severity and other relevant data was collected from medical records. Based on the data from proforma, in this study we considered seven major symptoms of UTI and were categorised into nil, mild, moderate and severe and accordingly scores were given and the symptoms are scored during the first visit and subsequent follow-ups.

The patients were initially treated with antibiotics for the infections and after the course of treatment they were administered with cranberry extract capsules for 60 days. The initial follow up is done after 2 weeks after starting cranberry treatment and the subsequent follow up was done after 1 month, 3 months and 6 months. Required information were collected using a suitably designed proforma during the first visit. Morisky Green Levine (MGL) scale was taken at the final follow up to assess the patient's medication adherence.

Wilcoxon signed rank test has been used for assessing effectiveness of treatment on study variables before and after treatment. Chi-square test for proportion difference was employed for finding significant risk factors for urinary tract infection. Chi-square test was used for assessing significant proportion differences in various classes. A calculated p-value less than 0.05 was considered to be statistically significant. All the analysis were carried out with the help of software SPSS version 22 for Windows.

RESULTS

Through this study we aimed to evaluate the efficacy of cranberry extract supplements in prevention of recurrent UTI in female patients. For this we selected 90 patients satisfying the inclusion and exclusion criteria and the final study included 84 patients for analysis.

Among the excluded 6 patients 4 patients lost follow up and 2 patients were reported to have the infection during treatment period. The patients with clinically diagnosed UTI were treated with antibiotics and after that they were given cranberry extract supplements for 60 days and were observed in our study.

Table 1: WSR test for assessing effectiveness of treatment on frequency of urination.

Frequent urination	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	38.1	45.2	54.8	73.8	84.5
Mild	8.3	21.4	36.9	20.2	8.3
Moderate	38.1	33.3	8.3	6.0	6.0
Severe	15.5	0	0	0	1.2
P value		0.000*	0.000*	0.002*	0.035*

*significant (p<0.05)

Table 2: WSR test for assessing effectiveness of treatment on urgency of urination.

Urgency	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	61.9	70.2	85.7	91.7	94.0
Mild	4.8	19.0	13.1	7.1	2.4
Moderate	25.0	10.7	1.2	1.2	3.6
Severe	8.3	0	0	0	0
P value		0.000*	0.000*	0.160 ^{ns}	1.000 ^{ns}

*Significant (p<0.05)

Table 3: WSR test for assessing effectiveness of treatment on painful urination.

Painful urination	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	39.3	47.6	71.4	84.5	91.7
Mild	7.1	27.4	17.1	10.7	2.4
Moderate	25.0	22.6	10.7	4.8	3.6
Severe	28.6	2.4	0	0	0
P value		0.000*	0.000*	0.002*	0.285 ^{ns}

*Significant (p<0.05)

Table 4: WSR test for assessing effectiveness of treatment on incomplete voiding.

Voiding difficulty	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	71.4	75	82	95.2	96.4
Mild	1.2	15.5	15.5	3.6	1.2
Moderate	25	9.5	2.4	1.2	2.4
Severe	2.4	0	0	0	0
P value		0.000*	0.000*	0.001*	1.000 ^{ns}

*Significant (p<0.05)

Table 5: WSR test for assessing effectiveness of treatment on lower abdominal pain.

Lower abd pain	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	11.9	17.9	48.8	75.0	89.3
Mild	3.6	39.3	44.0	17.9	0
Moderate	22.6	42.9	7.1	7.1	6.0
Severe	61.9	0	0	0	4.8
P value		0.000*	0.000*	0.001*	0.297 ^{ns}

*Significant (p<0.05)

Table 6: WSR test for assessing effectiveness of treatment on low back pain.

Low back pain	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	54.8	58.3	65.5	75.0	86.9
Mild	4.8	11.9	25.0	17.9	8.3
Moderate	22.6	29.8	9.5	7.1	4.8
Severe	17.9	0	0	0	0
P value		0.000*	0.000*	0.043*	0.001*

*Significant (p<0.05)

Table 7: WSR test for assessing effectiveness of treatment on hematuria.

Severity	BT (%)	DT1 (%)	DT2 (%)	AT1 (%)	AT2 (%)
Nil	52.4	94	97.6	100	95.2
Mild	28.6	6.0	2.4	0	3.6
Moderate	13.1	0	0	0	1.2
Severe	6.0	0	0	0	0
P value		0.000*	0.000*	0.043*	0.087 ^{ns}

*Significant (p<0.05)

Most patients were having the symptom abdominal pain and least percentage of selected patients were having the symptom of incomplete voiding. It is shown in Figure 1.

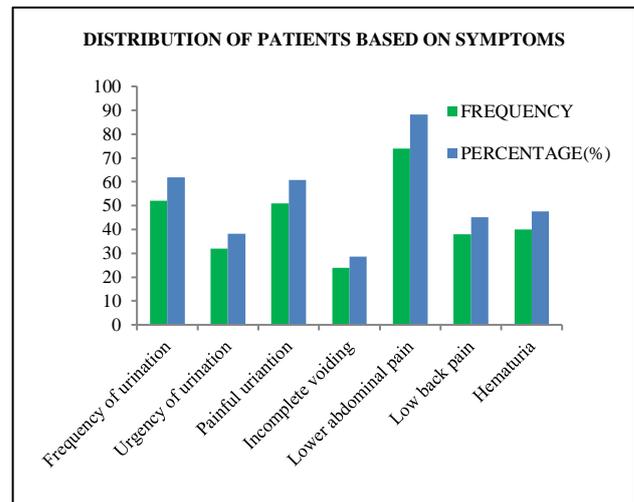


Figure 1: Distribution of patients based on the presentation of symptoms.

By the end of study the percentage of patients with no infection was raised to 86.9% from zero. It is represented in Figure 2. Thus the significance of cranberry therapy in prevention of recurrent UTI was seen evident. Regarding the medication adherence, the percentage distribution of people who don't stop medication after worsening of symptom, didn't stop the medication after improvement, not careless about time and not forget to take medicine was high which is represented in Figure 3. Thus they were having good medication adherence.

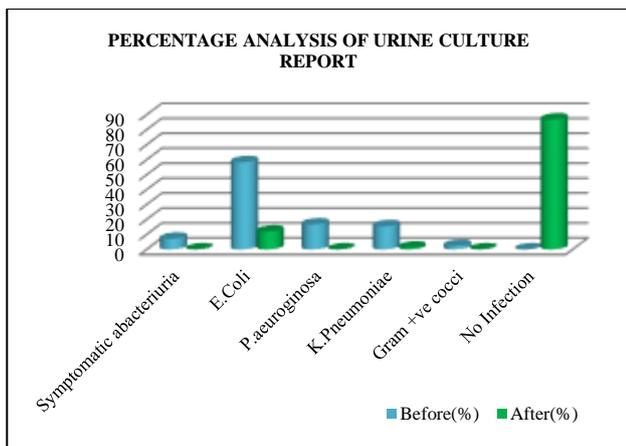


Figure 2: Percentage analysis of urine culture report.

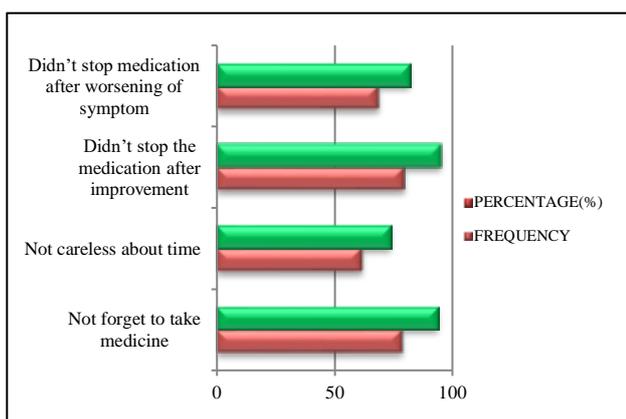


Figure 3: Percentage analysis of medication adherence of patients.

DISCUSSION

Urinary tract infections are common and among the most frequent medical conditions requiring outpatient treatment. Approximately 80% of all UTIs occur in women and 20% to 30% of women with a UTI will experience recurrence.¹⁶ Nowadays the incidence of recurrence is increasing and usually low dose antibiotic prophylaxis for several months are recommended. But antibiotic use is associated with the development of antibiotic resistance and the occurrence of side effects.¹⁷ No large-scale population data are available specifically for female patients with recurrent urinary tract infections regarding the risk factors, controlling measures and a good non antibiotic prophylaxis.¹⁸ Here we evaluated the efficacy of cranberry extract supplements in prevention of recurrent UTI in female patients.

Recurrent UTI is the occurrence of more than two UTIs in a year. Recurrent UTI can affect the health related quality of life of the patients badly and is considered as a significant public health problem.¹⁹ The observation is that the use of cranberry (*Vaccinium macrocarpon*) extract supplements resulted in a significant reduction in the recurrence. Cranberry contain two compounds with

anti-adherent properties that prevent fimbriated *E. coli* from adhering to uroepithelial cells in the Urinary tract. One is fructose which inhibits the Mannose sensitive fimbrial adhesions; and the other is proanthocyanidines that inhibits the mannose resistant adhesions of uropathogenic *E. coli*.²⁰⁻²²

The data on personal details (age, history of recurrence) and symptoms were collected from 90 UTI patient's medical records and direct interviews with the patient or bystander, analysed using appropriate statistical methods. Frequency and percentage were calculated as summary measures for categorical study variables while mean, SD, median and range were calculated as summary measures for continuous study parameters.

Detailed analysis were presented in the following sections:

Personal details of patients

In the section personal details such as age, history of recurrence, symptoms, co-morbid conditions were collected from medical records of the selected UTI patients or direct interview with the patient or bystanders and carry out a percentage analysis and it was observed that majority of the selected UTI patients were at an age group of 31-50 (42%), followed by 51-70 (38%), and then 18-30 (20%). Most of the patients enrolled in the study were having history of two to three times of recurrence in a year (72%). Also found that majority of patients were having co-morbidity of DM.

The studies focused towards the woman population are limited. Study conducted by Ahmed et al selected older adults aged above 65 for the study. They suggest that elder people are at high risk of developing recurrent UTI. Some studies suggest that after menopause women are at high risk of developing recurrent UTI because of lack of protective action by estrogen.²³ Study conducted by Uberos et al analysed the efficacy and safety profile of cranberry in infants and children with recurrent urinary tract infection.²⁴ It was the first randomized controlled double-blinded trial that demonstrates the safety of cranberry in infants and children. In our study we focused on women at the age group of 18-70.

Effectiveness of cranberry supplements in recurrent UTI

In 1984 Sobota observed that cranberry extract interferes with the adherence of p-fimbriated *E. coli* to the epithelium, demonstrating that this may be one of the main mechanisms underlying the anti-adhesion activity of cranberry.²⁵ Foo et al identified A-type proanthocyanidine trimers and pro-cyanidine dimers as being responsible for the anti-adhesion activity of cranberry. This suggest cranberries as alternate choice for antibiotic therapy.²⁶ The high incidence rate of recurrent UTIs and the development of antibiotic

resistance and side effects in response to the prophylactic antibiotic treatment makes it necessary to use another good alternative.

In the current study the clinical symptoms of the patients are identified and are scored as nil, mild, moderate and severe. For this, seven symptoms were selected which are: frequency of urination, urgency, burning pain or painful urination, incomplete voiding, lower abdominal pain, low back pain and hematuria. The symptoms were scored during the first visit and each follow up visits. Culture tests were performed for detecting the recurrence of infection. Wilcoxon signed rank test was used for assessing the effectiveness of treatment.

After analysis it was found that the cranberry supplements provide a significant reduction in the recurrence of infection. It was found that at the final follow up the percentage of patient with no reported recurrence was 86.9% and they were symptomatically better. The most commonly found uropathogen was *E. coli* (58.3%) followed by *P. aeruginosa* (16.7%), *K. pneumonia* (15.5%) and gram positive cocci (2.4%) were the least reported. 7.1% of patients were having symptomatic abacteriuria. Most of the studies conducted were comparative studies. A pilot study conducted by Ledda et al proved that cranberry are efficacious in preventing recurrent UTI.²⁷ In their study the grouped the patients into two. One group was provided with cranberry supplements and life style advice while the other group was given life style advice only. It concluded the efficacy of cranberry supplements. But the study follow up was only two months and it was too short for checking recurrence. The study published by McMurdo et al compared the effectiveness of cranberry extract with low dose Trimethoprim in the prevention of r UTIs in older women and it was found that trimethoprim have a very limited advantage over cranberry extract in the prevention of recurrent UTI in older women and had more adverse effect.²⁸ These data prove the advantages of cranberries over antibiotics for prophylaxis treatment. Wing et al conducted a randomized controlled pilot study on daily cranberry juice for the prevention of asymptomatic bacteriuria in pregnancy. The study data suggested that there might be a protective effect of cranberry ingestion against ASB and symptomatic UTIs in pregnancy.²⁹

Assessment of medication adherence of patients

A standard MGL questionnaire has used for assessing the medication adherence of the UTI patients. The questionnaire was provided at the final follow up. It contain four questions regarding the medication use of the patient. Each question measured based on a two point linked based scale ('yes', 'no'). The statistical analysis showed that 94 % of patients 'didn't forget to take the medication', 73.8% patients were 'not careless about the time of taking the medicine', 95.2% of patients 'didn't stop the medication even after the symptom got subsided' and 82.1% of patients 'didn't stop the medication even

after worsening of symptom'. Wilcoxon signed rank test showed that most of the patients were showing good compliance to the treatment provided.

The major limitations of our study were that the study population was quite small and it was having shorter duration which limited our study. We recommend further extensive studies involving more patients more objectives and comparative studies.

CONCLUSION

UTI are very high but data regarding the treatment of recurrent UTI are not much sufficient and the use of antibiotic for the prophylaxis was associated with the development of side effects and antibiotic resistance. This study had tried to evaluate the efficacy of cranberry extract supplements as an alternatives to antibiotics in prevention of recurrent UTI in female patients. The study concluded that the cranberry supplements are effective in the prophylactic management of recurrent UTIs. We also assessed medication adherence of the patients. The medication adherence of the patients were also good. Involvement of female patients having the previous history of recurrent UTIs, measurement of clinical symptom scoring system and proper testing during each follow ups were the main pillars of our study.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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