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Evaluation Effect of Combination Probiotics and Antibiotics in the Prevention of Recurrent Urinary Tract Infection (UTI) in Women

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ABSTRACT

UTIs are common in women, result in considerable morbidity and expense, and can be a vexing management problem for clinicians. We designed a randomized clinical trial study to investigate the efficacy of probiotic administration in addition to antibiotics for prevention of RUTI in women. This study was an RCT with RCT number IRCT2015090323871N1 and was approved by the Baqiyatallah University of Medical Sciences ethic committee. In this study, patients referred to the Baqiyatallah urology department with the diagnosis of UTI from April 2015 to April 2016 were included. The study 162 patients were randomized assigned in a 1:1 ratio to probiotic FamiLact capsules plus antibiotics or antibiotics alone. The intervention group was received to take one 500 mg probiotic capsule addition antibiotics every day for six month. 162 patients were evaluated for study participation. The mean ± SD age of the participants was 43.42 ± 10.85 years. In six month follow-up, 18 patients in the antibiotics alone group had the recurrence of infection and two patients in the probiotics plus antibiotics group had the recurrence of infection. In three months follow-up, 23 patients in the antibiotics alone group had the recurrence of infection and four patients in the probiotics plus antibiotics group had the recurrence of infection ($P<0.001$ and $P<0.001$ respectivly) (Table 3). There was no significant difference between two groups regarding the incidence of recurrence of infection after six follow-ups ($P=0.37$). Probiotics have confirmed ability to prevent and treat some infections. Efficient use of probiotics has the potential to decrease patients' exposure to antimicrobials. Available probiotics appear safe but should probably be avoided in patients at high risk for septicemia.

Keywords: Recurrent Urinayr tract infection (UTI), probiotic.

INTRODUCTION

UTIs are common in women, result in considerable morbidity and expense, and can be a vexing management problem for clinicians[1]. Given the vast number of cases of UTI occurring each year and the high recurrence rate, it is critical that preventive methods be available (2, 3). For the most part, current prevention involves the use of antibiotics[4, 5]. In complicated cases, for example, indwelling-catheterized male and female patients, antibiotic therapy is given daily to prevent an infection that could subsequently lead to bacteremia and death[6].

UTI is one of the most common bacterial infections, affecting 20% of women between 20 and 56 years of age per annum. About 25% these women will develop a recurrence 3–6 months, and 27% will experience a recurrence within 6–12 months)

UTI is a highly common patient problem among young healthy women and results in considerable morbidity and health care cost[8-10]. UTI

adds to the duration and cost of hospital admission and nosocomial uropathogenic form a reservoir of antibiotic-resistant bacteria[10].

Although most cases of UTI can be treated easily with recently developed broad-spectrum antibiotics, these antibiotics do not change a patient's susceptibility to recurrences. The patient's quality of life is affected, and many women become frustrated by the repeated use of antimicrobial agents whose effectiveness is diminishing owing to their increasing antimicrobial resistance[11].

Long-term antibiotic prophylaxis is the most common method for managing recurrent UTI. However, antibiotic use leads to the increased presence of drug-resistant organisms, and many patients suffer from yeast vaginitis as a result of the disruption of normal levels of intestinal and vaginal flora[12]. In such cases, it has been noted that probiotics, which are defined as living microorganisms that can be administered to promote the health of the host by treating or preventing disease, can be used as an alternative preventative approach[13]. The risk of recurrent UTI in women has been demonstrated to be reduced by the use of prophylactic antimicrobials[14].

Recently the advantages and safety of probiotics have been evaluated in the area of gastroenterology from constipation to antibiotic-associated diarrhea, irritable bowel syndrome to inflammatory bowel disease; however, the results were controversial[15].

However, since probiotics have long been studied for use in the urogenital tract, skin, nasopharynx, and other sites, our preferred definition is "microorganisms that confer health benefits to the host." Application of such probiotic organisms can be via oral ingestion, vaginal insertion, or other means, such as ointments and creams[16].

Many publications describing the relationships between lactobacilli and UTI are available[17]. However, the effectiveness of probiotics on recurrent UTI is still inconclusive. There have been some evidence that probiotics can prevent colonization of uropathogenic bacteria and have potential benefits on prevention of renal injury-inducing UTIs[18].

We designed a randomized clinical trial study to investigate the efficacy of probiotic administration in addition to antibiotics for prevention of RUTI in women.

MATERIAL AND METHODS

This study was an RCT with RCT number IRCT2015090323871N1 and was approved by the Baqiyatallah University of Medical Sciences ethic committee. In this study, patients referred to the Baqiyatallah urology department with the diagnosis of UTI from April 2015 to April 2016 were included. The cases were women who had symptomatic UTI (symptoms of urination frequency, urination urgency, dysuria, hematuria, nocturia, fever, and back or flank pain). The women entered the study within two weeks of the culture-confirmed UTI episode. Subjects were excluded from the study if they received long-term antimicrobial prophylaxis at the time of the index UTI.

Exclusion criteria were current complicated cystitis or uncomplicated pyelonephritis; a history of urologic abnormality or renal calculi; recent sexually transmitted infection, risk factors for STI and personal immunodeficiency virus (HIV) infection; pregnancy or within two months of pregnancy; lactation; menopause; diabetes, HIV infection, or other immune compromised state; drug or alcohol abuse; abnormal pelvic examination results; and persistent symptoms and/or pyuria after treatment of the included UTI.

This study was an RCT with RCT number IRCT2015090323871N1 and was approved by the Baqiyatallah University of Medical Sciences ethic committee. In this study, patients referred to the Baqiyatallah urology department with the diagnosis of UTI from April 2015 to April 2016 were included. The study 162 patients were randomized assigned in a 1:1 ratio to probiotic FamiLact capsules plus antibiotics or antibiotics alone. Randomization was stratified using a random table number. Informed consent was obtained from all patients before enrollment.

The intervention group was received to take one 500 mg probiotic capsule addition antibiotics every day for one month. Probiotic capsules was Familact, Zisttakhmir Co, Tehran, Iran that contained 7 × 109 colony forming unit (CFU) Lactobacillus Casei, 2 × 109 CFU Lactobacillus Acidophilus, 1.5 × 109 CFU Lactobacillus Rhamnosus, 2 × 108 CFU lactobacillus Bulgaricus, 2 × 1010CFU Bifidobacterium Breve, 7 × 109 CFU Bifidobacterium Longum, 1.5 × 1010 CFU Streptococcus Thermophilus as well as other ingredients such as fructooligosaccharide (as prebiotic)[19].

The protocol was evaluated by the Ethical Committee of the Baqiyatallah University of Medical Sciences and was found to be ethically acceptable. Participant signed the informed consent indicating the aim of study and interventions. Bacteriuria was considered when a single bacterial species was isolated in concentrations equal or greater than 100000 colony forming units/ml of mid-stream clean catch urine samples.

Preoperative evaluation included demographic data, medications, surgical and medical history of the patients. Preoperative evaluation included infection, and recurrence of infection during the one, three and six months postoperative follow-up.

Descriptive statistics were calculated for the presented data. Chi-square test and Fisher's exact test was used for determining the association between qualitative variables. Comparison between the groups was made using the non-parametric Mann-Whitney test. The Kolmogorov–Smirnov test was used for normality of the data. The data was analyzed by SPSS 20 software (SPSS, Chicago, IL, USA). The significance level was considered less than 0.05.

RESULTS

162 patients were evaluated for study participation. The mean ± SD age of the participants was 43.42 ± 10.85 years. Table 1 depicts demographics of the study samples. There was no statistically significant difference between the two groups regarding age, the onset of disease, job and marital status (P=0.153, P=0.13, P=0.23 and 0.41 respectively) (Table 1).

The mean ± SD infection count of the antibiotics group was 3.88 ± 1.03 and in the probiotics plus antibiotics group was 3.76 ± 0.98 in one year, and there was no significant difference between two groups (P=0.48). In total, 143 (88.8%) of patients had E.coli infection. There was no significant differences in the probiotics plus antibiotics group compared

Table 1: Demographic of patients in two groups

P-value	Total	Antibiotics +probiotics	Antibiotics	Items
0.85	125/37	63/18	62/19	Marital status (M/S)
0.15	43.42 (±10.85)	42.21 (±10.71)	44.66 (±10.92)	Age (mean (±SD))
0.13	3.68 (±1.86)	3.46 (±1.79)	3.90 (±1.92)	The onset of disease

Table 2: Rate of types of infections in two groups

P-value	Total	Antibiotics +probiotics	Antibiotics	Items
0.203	143	70	73	E.coli
	7	2	5	Klebsiella
	12	9	3	Staphylococcus aureus
	162	81	81	Total

to antibiotics alone group in types of infections (P=0.203) (Table 2).

In one month follow-up, 18 patients in the antibiotics alone group had the recurrence of infection and two patients in the probiotics plus antibiotics group had the recurrence of infection. There was a significant decrease of recurrence of infection in the probiotics plus antibiotics group compared to antibiotics alone group (P<0.001) (Table 3).

In three months follow-up, 23 patients in the antibiotics alone group had the recurrence of infection and five patients in the probiotics plus antibiotics group had the recurrence of infection. There was a significant decrease of recurrence of infection in the probiotics plus antibiotics group compared to antibiotics alone group (P<0.001) (Table 3).

There was no significant difference between two groups regarding the incidence of recurrence of infection after six follow-ups (P=0.37) (Table 3).

DISCUSSION

In this study, the significant difference was observed between antibiotic alone and probiotic plus antibiotic prophylaxis in the prevention of UTIs after one consumption of probiotic. Albeit antibiotics such as Trimethoprim–sulfamethoxazole, Amoxicillin-clavulanic acid and Cephalosporin are extensively utilized in the therapy of UTI, the efficient method for prevention of UTI is still obscure[20]. To date, antibiotic prophylaxis and surgical correction of VUR have accepted methods for prevention of UTI[15]. Costs and adverse effects of these methods and discussions about their efficacy in prevention of RUTI have encouraged the researchers to find alternative methods[14-16]. Although antimicrobial agents are quite effective at providing a clinical cure for UTI, they do not change a patient's susceptibility to recurrences[20]. The use of antimicrobial agents results in yeast vaginitis as a consequence of the disruption of the normal levels of intestinal and vaginal flora and the development of antimicrobial resistance[21]. In fact, resistance rates to trimethoprim-sulfamethoxazole in the USA and Canada and fluoroquinolones in Spain among E. coli isolates are both 18%[21]. Current societal trends in healthcare show a definite movement toward the use of natural remedies and away from chemotherapeutic regimens[22]. Therefore, a new strategy for the prophylaxis of recurrent UTI in women should be developed. In such cases, it has been noted that probiotics, which are defined as living microorganisms that, when applied in sufficient quantities, confer a health benefit to the host, can be used as an alternative preventative approach[23]. Recently natural methods have gained popularity among scientists for the management of human diseases[24]. Very few researchers assessed the efficacy of cranberry juice in the prevention of UTI in women and children[15-17]. They reported that consumption of cranberry juice prevents recurrences of UTIs in females. It has been recommended that cranberry juice has an efficient performance in UTI prevention by the modulation of the microbial flora of the intestinal and urogenital situation[15].

Studies utilizing Lactobacillus-containing products such as yogurt have been largely unsuccessful in demonstrating successful colonization with the exogenous strain and influencing clinical outcomes related to bacterial vaginosis[24]. However, it has been reported that Lactobacillus vaginal capsules are effective in treating bacterial vaginosis and in reestablishing a Lactobacillus-predominant flora[25]. Also, there are some publications on the preventative effect

Table 3: Rate of recurrence of infections in two groups

P-value	Total	Antibiotics +probiotics	Antibiotics	Items
<0.001	30	18	2	One month follow-up
<0.001	28	23	5	Three months follow-up
0.521	51	28	23	Six months follow-up
	99	69	30	

of Lactobacillus vaginal suppositories on recurrent UTI[26]. Reid *et al.* have demonstrated that Lactobacillus vaginal suppositories are safe and may be effective in reducing the recurrence of UTI[27]. Conversely, Baerheim *et al.* have shown that uncertainty exists as to whether the vaginal administration of lactobacilli decreases the infection incidence in cystitis-prone women[28]. Since the effectiveness of probiotics on recurrent UTI is still inconclusive, a study to verify the safety and effectiveness of probiotics against recurrent UTI were performed.

On the other hand, studies are suggesting that probiotics (Lactobacillus rhamnose GR-1 and L. reuteri RC-14) can prevent the colonization of uropathogenic bacteria[29]. Moreover, there are discussions on the usefulness of probiotics in inflammatory bowel disease and constipation. These controversial effects may be due to strains that were studied and dosage and duration of probiotic supplementation. Therefore further studies were suggested. Reid *et al.* in 1985, assessed the efficacy of lactobacilli in prevention of UTI in rats for the first time[30]. They injected five strains of periurethral uropathogenic into the urinary bladder and then instilled an isolate of Lactobacillus casei GR1 within rat's bladders. They remarked the prevention of colonization in 84% of animals. Useful probiotic strains for the UTI prevention can produce bacteriocin, biosurfactant barrier, and hydrogen peroxide and adhere to the positions of uropathogenic bacteria. With such mechanisms, they can interfere with the colonization of uropathogenic. Osset *et al*[31] observed that Lactobacilli from hemagglutination group III had the greater capacity to block uropathogenic adherence than other strains. The most susceptive uropathogens were Pseudomonas aeroginosa PA5, Klebsiella pneumonia KP7 and Staphylococcus aureus SA11, while Proteus mirabilis PM1 was the extremely resistant uropathogenic to blockage. Similarly, based on the results of this study no infection by Pseudomonas aeruginosin and Klebsiella pneumonia was recorded in children who acquired probiotic+antibiotic prophylaxis. A human clinical trial reported that instillation of L. rhamnose GR-1 or L. fermentum RC-14 through the vagina reduced the recurrence of UTI in women. Another study by Kontiokari *et al.* reported that consuming L. acidophilus yogurt for at least three times per week was associated with significant decrease in episodes of UTI breakthrough. Management of vaginal suppositories containing the strain Lactobacillus crispatus GAI 98322 can significantly decrease the recurrence rate of UTI in women, without any complication[32].

In a study showed that vaginal suppositories with L. crispatus GAI 98332 could decrease the recurrence of UTI significantly without any adverse complication during treatment[33]. Our study is in agreement with this results. The reason why the study demonstrated a significant reduction might be because the most suitable strain was selected. L. crispatus is readily isolated from the vagina of healthy women and is nearly universal in its ability to produce hydrogen peroxide and to bind to vaginal epithelial cells[34]. They report that the hydrogen peroxide production of three L. crispatus strains was measured, resulting in the selection of strain GAI 98332 because it produced the highest level of hydrogen peroxide[29].

It is believed that the pathogens of UTI ascend from the rectum to the vagina and then to the urinary bladder. This process is mediated by bacterial adherence and is not altered by antibiotic use[19]. This leads to the investigation that the colonization of pathogens in the vagina is necessary for recurrent cystitis to occur. In fact, the flora of the urogenital tract is abnormal in patients with recurrent UTI compared with those of healthy women. The use of probiotics to heal the normal vaginal flora and provide a competitive bacterial barrier is becoming increasingly acceptable[9-11].

Probiotics are Gram-positive rods; essentially facultative or severe anaerobes that have a particular growth requirement. They prefer an acidic environment and help create one by producing lactic and other acids[26]. Lactobacilli have not been associated with disease, and for more than 100 years have been regarded as non-pathogenic members of the intestinal and urogenital floras[29].

Doederlein first recognized the role of lactobacilli in the maintenance of vaginal health in the late 18th century[23]. Therefore, the concept of administering exogenous Lactobacillus for maintaining optimal vaginal microflora is more than a century old. Vaginal lactobacilli protect the

female urogenital tract from pathogen colonization and, therefore, can contribute to the prevention of genitourinary tract infection. Many studies have been published describing the relationships between bacterial vaginosis and lactobacilli[18].

Contrary to many studies on the application, safety, and efficacy of probiotic strains for prevention of UTI in women[14]. The concept of probiotics is simple in some ways, but the critical issues are the selection of the optimal strains, verification of the necessity for, and mechanisms of, certain factors in the interference with pathogens and clinical proof that there is merit to the theory. In general terms, protective roles of vaginal lactobacilli have been identified for lactobacilli to be effective probiotic organisms[23]. Lactobacilli and the hydrogen peroxide that they produce are increasingly recognized as essential components of a healthy microflora environment. Hydrogen peroxide is toxic to many microorganisms at concentrations that are typical in the vaginal fluid and thus provides an intrinsic protective mechanism in the vagina. Also, recent studies have established that L. crispatus and L. jensenii are two of the most readily isolated microorganisms from vaginal flora[35].

CONCLUSION

Probiotics have confirmed ability to prevent and treat some infections. Efficient use of probiotics has the potential to decrease patients' exposure to antimicrobials. Available probiotics appear safe but should probably be avoided in patients at high risk for septicemia. It is suggested that future investigations focus on determining the optimal dosage, duration, and mode of probiotics delivery for establishing vaginal and/or periurethral colonization. Furthermore, it is proposed that prospective randomized studies be performed.

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