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Pilot Study on the Evaluation of the Effectiveness and Tolerability of an Enterosorbent (POLISORB) Associated with a Probiotic for the Prevention of Recurring Cystitis

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Abstract

Objective: The use of silicon dioxide (POLISORB) causes the elimination of pathogenic germs, promoting the normal formation of intestinal flora (eubiosis) with the insertion of a probiotic. This phenomenon may formulate a new approach to preventing recurrent cystitis.

Materials and Methods: This is a multicentric pilot study. All women aged between 18 and 75 and with at least 3 episodes in 1 year or 2 episodes in 6 months of documented bacterial cystitis were enrolled. Polisorb has been administered 2 tps three times a day for 7 days in the first month and 2 tps twice a day for 5 days in the second and third month (1 h between meals and 2 h from taking drugs). Probiotic has been administered 1 tablet twice a day for twenty days a month for 3 months. The effectiveness of the treatment has been assessed considering the reduction in the number of urinary tract infections and the improvement of subjective symptoms.

Results: Between September 2018 to July 2019, 45 patients were enrolled in the present study. 17 patients presented UTI at the first urine culture, but only 4 patients showed UTI at the urine culture at three months. 34 patients were completely asymptomatic at the end of the study. No patient experienced side effects and 38 patients were very satisfied about the study protocol.

Conclusion: This study confirms that Polisorb is safe and effective for the treatment of UTI and recurrent cystitis.

Keywords: Enterosorbent; Probiotic; Recurrent cystitis; UTI

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Introduction

Urinary Tract Infections (UTI) represent the third most frequent infection after those of the respiratory and gastrointestinal tract [1] with, in addition to serious discomfort in the female population [2]. UTI are the infections with the heaviest impact both on welfare budgets and on the quality of life of these patients. UTI are defined as the presence of bacteria in the genitourinary tract associated with clinical symptoms and signs. UTI are classified from an anatomical point of view in lower (cystitis, in case of bladder involving), or upper infections (pyelonephritis, in case of renal parenchyma involving), and about their severity in uncomplicated (patient without structural or functional abnormalities, not pregnant, without catheter) or complicated [3].

Cystitis is defined as a symptomatic acute or chronic bacterial infection of the lower urinary tract, which causes dysuria and urgency, sometimes hematuria and suprapubic pain not always associated with passing the urine [2,4].

Single UTI episodes are very common, especially in adult women, with women showing a 50-fold higher rate of infection than adult men [3]. Recurrent Urinary Tract Infections (R-UTI) are defined as three or more episodes in 12 months or two or more episodes in 6 months [1,5,6]. Age and menopause can contribute to R-UTI for urogenital involution due to the loss of estrogen and worsening constipation. Cystitis after sexual intercourse (postcoital cystitis) represents 60%

of recurrent cystitis, which is also present in 40% of postmenopausal women (OR=3.42) [7]. Gender vulnerability is clear: in adulthood, recurrent cystitis is reported in 1 in 3 women, while in men the ratio is 1:20 [8].

In the literature it is possible to identify some predisposing factors.

Metabolic factor: Insulin-dependent diabetes is an important predisposing factor for R-UTI (with OR range of 2.0 to 3.4, between different studies) [9-12]. Relapses and reinfections have been reported in 15.9% of women with diabetes mellitus 7.1% against 2.0% of women without diabetes. More recent research confirms that obesity and diabetes increase the risk of R-UTI [13].

Bladder factor: The urothelium is coated with Glycosaminoglycans (GAG) and proteoglycans. This acellular functional layer, defined as "bladder lining" is the first line of defense of the bladder [14], guarantees the impermeability of the surface of the bladder to urine ions and bacteria, neutralizes toxic metabolites, inhibits the passage of small molecules; inhibits the adhesion of some germs and the formation of microcrystals. A deficient lining of the bladder can lead to the passage of urinary bacteria towards the innermost structure of the urothelium until it reaches the interstitial space. Activation of mast cells and the consequent pro-inflammatory cascade of events can cause damage to the bladder barrier [14].

Urethral factor: The urethral mucosa with the layers of the submucosa and muscularis should ensure a good "sealing effect" of the urethral lumen, thus preventing ascending infections during sexual intercourse. This protective mechanism is partially influenced by estrogen and partially by androgens and can become defective after menopause [14].

The vaginal pH and the vaginal ecosystem: Estrogens are essential for maintaining the normal vaginal ecosystem with Lactobacilli, which favor a vaginal pH of 4.0 to 4.5. A vaginal pH of 5 or more is associated with bacterial vaginosis, vaginitis and cystitis.

Intestinal factor: *Escherichia coli* (*E. coli*) is the most common microbial agent (80% of the cases) involved in UTI, due to a bacterial transmigration from the bowel [15,16]. An altered intestinal flora can lead to the overgrowth of enterobacteria, such as *E. coli*. Irritable bowel syndrome and the increased passage ("translocation") of intestinal germs through intestinal cells (barrier violation) is a predisposing key for R-UTI [17-19]. Constipation, which worsens with age and menopause, is another predisposing intestinal factor.

Enterosorbents are absorbent drugs designed for the agglomeration of toxic substances, pathogens and metabolites of various species in the gastrointestinal tract as well as for their removal. Among the enterosorbents, the one with the least side effects is silicon dioxide. Polisorb® [20] is a non-selective and multifunctional enterosorbent based on highly dispersed silicon dioxide (chemical formula SiO_2). It has an absorption capacity of 300 mg/g and has excellent absorbent and detoxifying properties. In the gastrointestinal tract, Polisorb® is capable of binding endogenous and exogenous substances of any molecular mass, such as bacteria, viruses, toxins, allergens and other harmful substances respectively.

Recurrent cystitis is caused by the presence of a high pathogenic bacterial load in the gastrointestinal reservoir. Even the use of antibiotic therapy and probiotics does not always manage to reconstitute a correct intestinal eubiosis and this situation favors the abnormal regrowth of pathogenic bacteria in exorbitant numbers (dysbiosis) such as to encourage new episodes of cystitis [21].

Aim

The use of silicon dioxide (Polisorb®) causes the elimination of pathogenic germs, promoting the normal formation of intestinal flora (eubiosis) with the insertion of a probiotic [21]. This phenomenon may formulate a new approach to preventing recurrent cystitis.

Materials and Methods

From September 2018 to July 2019, consecutive patients referred to the Pelvic Floor Unit for recurrent urinary tract infection were included in the study. This is a multicentric pilot study on safety and effectiveness of enterosorbent to prevent R-UTI. The institutional review board approved the study protocol. All patients must be aged between 18 and 75 years old, and with at least 3 episodes in 1 year or 2 episodes in 6 months of documented bacterial cystitis were enrolled. A wright informed consent was obtained from each patient before to start the study protocol. For this study, the following exclusion criteria were established:

- Intolerance towards one or more components of POLISORB® or NATURAFLORA PLUS® (probiotic);

- Pregnancy, diabetes mellitus, primary and secondary immunodeficiencies, therapy with antibiotics and corticosteroids, any serious disease or chronic condition that may interfere with the compliance of the study, psychiatric disorders;

- Bacterial cystitis in progress (to be treated before the study with antibiotic therapy and with subsequent negative urine culture).

This first visit included assessment of the following features: weight, height, parity, period, menopausal status, cigarettes per days, sexual intercourse, risk factors (diabetes, immunodeficiencies, pregnancy, therapy with antibiotics and corticosteroids, any serious disease or chronic condition, psychiatric disorders), symptoms (asymptomatic, dysuria, frequency, urgency, cloudy urine, smelly urine, hematuria, pelvic pain).

Polisorb® has been administered 2 doses three times a day for 7 days in the first month and 2 doses twice a day for 5 days in the second and third month (1 h between meals and 2 h from taking drugs). Probiotic has been administered 1 tablet twice a day for twenty days a month for 3 months. The effectiveness of the treatment has been assessed considering the reduction in the number of urinary tract infections and the improvement of subjective symptoms.

Urinary culture was performed at the beginning of the study (this one must be negative to start the study) and at 3 months and 6 months to test the effectiveness of Polisorb®.

The primary end point was the number of R-UTI during the three months of treatment and the following three months of observation. A UTI episode was defined in the form of significant bacteriuria as $>10^5$ CFU/ml of midstream urine with or without clinical symptoms.

The secondary end points were symptoms reduction and patient's satisfaction.

The change from baseline of the urinary symptoms was analyzed using the Fisher exact test. Statistical significance was set at the level of $p<0.05$.

Table 1: Demographic characteristics of patient's population.

Age (average), n (sd)	57.71 ± 16.224
BMI (average), n (sd)	25.04 ± 4.369
Parity (average), n (sd)	1.69 ± 0.996
Menopause, n (%)	31 (68.9)
Smokers, n (%)	6 (13.3)
Sexual intercourse, n (%)	31 (68.9)

sd: Standard Deviation

Results

Sixty patients were enrolled in the present study. Fifteen patients met exclusion criteria and were excluded by the statistical analysis. Demographic characteristics of the remaining 45 patients are reported in Table 1. Most patients were in menopause and with regular sexual intercourse. Only six patients were smokers.

Only 4 patients were asymptomatic at the beginning. Dysuria was the most common symptom, present in 32 patients. The average number of symptoms associated with UTI decreased significantly at the end of the study period: In particular, dysuria episodes have decreased (32 *vs.* 10, p<0.01 at 3 months and 32 *vs.* 6, p<0.01 at 6 months), frequency (17 *vs.* 3, p<0.01 at 3 months and 17 *vs.* 4, p<0.01 at 6 months) and urgency (12 *vs.* 0, p<0.01 at 3 months and 12 *vs.* 0, p<0.01 at 6 months). Study results are reported in Table 2. Twenty-six and thirty patients become asymptomatic respectively at 3 months and 6 months. Nine patients referred a positivity on the urine culture at 3 months, while at 6 months only 4 patients referred UTI. No adverse effects and complications were reported upon treatment. In no case was it necessary to stop the treatment. *E. coli* was the most common pathogen present in the urine culture. The difference in terms of urine culture at 3 months and 6 months is not statistically significant. Patients and medical judgement were extremely positive at 3 months and 6 months as reported in Table 2.

Discussion

UTI are the most common infections in humans. *E. coli* is the most common uropathogen causing UTI, followed by Proteus and *Klebsiella* species, enterococci, Group B streptococci and *Pseudomonas aeruginosa* [22]. Guidelines suggest to take products based on local estrogen, cranberry, D-mannose or lactic ferments to try to reduce recurrent infections [23]. However, there is no standardized evidence to choose one therapy rather than another because of the lack of long-term randomized studies.

Another cause of UTI is the neurogenic bladder due to a reduction of the local immune defenses, an impairment lower urinary tract function, and to the bladder management (intermittent catheterism). Due to the high use of antibiotics, and therefore the increase in resistant bacteria, it becomes very important to adopt preventive measures such as adequate water intake, rhythm in urinary voiding and non-antibiotic prophylaxis (e.g., cranberry, urine acidifiers, probiotics) [6,24].

For this reason, in literature, are reported a lot of study focused on alternative therapies for R-UTI.

D-mannose has a documented effectiveness and safety in treating and preventing UTI [25]. *In vitro*, D-mannose binds and blocks FimH adhesins positioned on the tip of type 1 bacterial fimbriae. D-mannose acts as a competitive inhibitor of FimH that, during bacterial colonization, binds to the glycoprotein-containing carbohydrate receptors on the urinary epithelium [26].

In a recent study on 78 patients with R-UTI the administration of D-mannose plus salicin and lactobacillus acidophilus showed a significant reduction in Visual Analogic Scale (VAS) score (p=0.001) and in daily frequency (p=0.001). A reduction of incontinence episodes in patients was observed, too. Authors conclude that this therapeutic approach combining D-Mannose with Salicin (acute treatment) and *Lactobacillus acidophilus* La-14 (maintaining treatment) was effective in symptomatic bacterial UTI [26].

Cranberry represents another alternative strategy for the prophylaxis of recurrent UTI. Cranberries were being used as a medicine by Native Americans before 1620 AD and have been used as a urinary antiseptic for more than 200 years [3].

Nowadays, a lot of study shows that the dietary intake of berry fruits has a positive impact on human health and disease [27]; cranberry contribute to fight UTI preventing bacterial adherence to uroepithelial cells. This evidence was reported both *in vitro* and *in vivo* studies [28,29].

In humans, the dose recommended of cranberry necessary to

Table 2: Evolution of symptoms, positivity of urine culture, use of antibiotics and effectiveness in the study period at the beginning, at 3 months and 6 months.

	Beginning	3 months	*p*	Beginning	6 months	*p*	3 months	6 months	*p*
No symptoms, n (%)	4 (8.9)	30 (66.7)	<0.01	4 (8.9)	34 (75.6)	<0.01	30 (66.7)	34 (75.6)	n.s.
Dysuria, n (%)	32 (71.1)	10 (22.2)	<0.01	32 (71.1)	6 (13.3)	<0.01	10 (22.2)	6 (13.3)	n.s.
Frequency, n (%)	17 (37.8)	3 (6.7)	<0.05	17 (37.8)	4 (8.9)	<0.05	3 (6.7)	4 (8.9)	n.s.
Urgency, n (%)	12 (26.7)	0 (0)	<0.05	12 (26.7)	0 (0)	<0.05	0 (0)	0 (0)	n.s.
Cloudy urine, n (%)	10 (22.2)	0 (0)	<0.05	10 (22.2)	0 (0)	<0.05	0 (0)	0 (0)	n.s.
Smelly urine, n (%)	11 (24.4)	4 (8.9)	n.s.	11 (24.4)	4 (8.9)	n.s.	4 (8.9)	4 (8.9)	n.s.
Hematuria, n (%)	6 (13.3)	0 (0)	<0.05	6 (13.3)	0 (0)	<0.05	0 (0)	0 (0)	n.s.
Pelvic pain, n (%)	8 (17.8)	6 (13.3)	n.s.	8 (17.8)	0 (0)	<0.05	6 (13.3)	0 (0)	<0.05
Urine culture positive, n (%)	0 (0)	9 (20.0)	-	0 (0)	4 (8.9)	-	9 (20.0)	4 (8.9)	n.s.
Use of antibiotics, n (%)	-	8 (17.8)	-	-	4 (8.9)	-	8 (17.8)	4 (8.9)	n.s.
Effectiveness (medical opinion), n (%)	-	35 (77.8)	-	-	36 (80.0)	-	35 (77.8)	36 (80.0)	n.s.
Effectiveness (patient opinion), n (%)	-	34 (75.6)	-	-	38 (84.4)	-	34 (75.6)	38 (84.4)	n.s.

The result is significant at p<0.05. n.s.: Not Significant

prevent UTI is 300 mL of cranberry juice (36 mg of proanthocyanidins) [30]. An important randomized, double-blind *vs.* placebo multicentre study on 32 volunteers from Japan, Hungary, Spain, and France has evaluated the dosage regimes and collection time-periods following ingestion of a cranberry (18 or 36 mg of proanthocyanidins). Authors concluded that administration of proanthocyanidins-standardized cranberry powder at dosages containing 72 mg of proanthocyanidins per day in two split doses of 36 mg twice days may reduce bacterial adhesion and virulence in the urinary tracts [31].

A recent review showed that all the trials published about cranberry use in the reduction of R-UTI reported a statistically significant reduction of episodes with the exception of one trial [3].

Whortleberry juice, that contains proanthocyanidin and ascorbic acid, has been reported as effective on preventing R-UTI through its antioxidant properties [32,33].

Schiavi et al. [34] showed the combined effect of hyaluronic acid, chondroitin sulfate, turmeric and acorn on the prevention of R-UTI; 98 women were enrolled and investigated about pelvic pain, urinary frequency, and urinary urgency using the UTI Symptom Assessment questionnaire. The results showed significant reductions in symptoms in the intervention group.

Other plants used as medicament for UTI is Seidlitzia rosmarinus (eshnan), a perennial shrub belonging to the Chenopodiaceae family [35]. The elements present in this plant are protein, high levels of sodium carbonate, copper, saponin, zinc, iron, manganese, potassium, magnesium, and calcium [36-38]. This plant has diuretic, antiseptic, antibacterial, anti-inflammatory, and anti-urinary retention properties [39,40].

Kamalifard et al. [40] reported that *eshnan* is safe and effective to reducing the incidence of episode of R-UTI and its clinical symptoms over 2, 4, and 6 months of the study in women of reproductive age.

A clinical trial showed that Cornelian cherry (Cornus mas) is effective to prevent R-UTI when compared to placebo and nitrofurantoin. The results showed a significant reduction in positive urinary cultures and in burning sensation [41].

Ospemifene was evaluated in 39 patients to reduce R-UTI in a recent study, too [23]. This is the first Selective Estrogen Receptor Modulator (SERM) which has a demonstrated estrogen against effect on the vaginal epithelium. Authors reported that only two patients experienced one new UTI episode and the mean number of positive urine culture decreased significantly after 6 months (3.65 ± 2.12 *vs.* 0.25 ± 0.17, $p<0.01$). The mean number of urinary infection symptoms decreased significantly after treatment. No adverse effects were reported, and the total success rate was the 92.3% after 6 months. Authors concluded that ospemifene is a valid alternative with excellent tolerability for the UTIS prevention in postmenopausal patients [23].

Conclusions

To our knowledge, this is the first study that investigates the use of Silicon Dioxide (SiO_2) in patients with R-UTI. In literature there are not comparative or randomized prospective study about the use of Polisorb® in R-UTI. The use of Polisorb® is principally recommended for gastrointestinal pathologies such as diarrhea, intoxications, dysbiosis and intestinal bowel disease.

As previously reported, in R-UTI the use of antibiotics is not always effectiveness, principally in case of multi drugs resistance. For this reason, a lot of study reported the necessity to prevent R-UTI also by using supplements; their activity is mainly aimed at preventing colonization of the bladder wall by bacteria. Polisorb® is the first one reported to be able to prevent R-UTI by reducing the bacterial transmigration by the bowel. Our data about the number of positive urine culture at 3 months and 6 months (9 *vs*. 4, respectively, p not significant) confirm the effectiveness of Polisorb® to prevent R-UTI also after the end of the treatment. In conclusion, this study confirms that Polisorb® is safe and effective for the treatment of UTI and recurrent cystitis. Furthermore, future prospective randomized study will be necessary to confirm this data.

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