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A New Approach to the Treatment of Uncomplicated Cystitis: Results of a Randomized Placebo-Controlled Clinical Trial

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Key Words
Cystitis · Urinary tract infections · Recurrence · Clinical trial

Abstract
Objective: To assess the efficacy and safety of a new medical device (MD; a capsule whose main component is a cross-linked protein) in the prevention of uncomplicated cystitis recurrences. ***Methods:*** Adult women with acute cystitis symptoms and a ciprofloxacin-susceptible isolate in urine culture were included in a randomized, double-blind clinical trial. Patients were treated with ciprofloxacin 500 mg/day and 1 capsule/day or matched placebo for 5 days, 1 capsule/day or placebo for 15 additional days, and 2 additional cycles of 1 capsule/day or placebo for 15 days on months 1 and 2 after initial treatment. ***Results:*** No recurrence was observed after the first month of follow-up in the MD-treated group. In addition, symptomatic recurrence was reduced by 19.4% compared with placebo after 6 months. ***Conclusions:*** The new MD can help prevent the recurrence of uncomplicated cystitis as well as help to reduce antibiotic use in management of urinary tract infection in women.

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Introduction

Urinary tract infections (UTIs) are one of the most prevalent bacterial diseases. They represent significant morbidity and resource use [1] because they involve visits to primary care and emergency departments as well as antibiotic therapy [2]. About 90% of community-acquired uncomplicated UTIs are caused by Gram-negative bacteria of fecal flora from the *Enterobacteriaceae* family, predominantly *Escherichia coli* [3]. These bacteria can colonize the genital area, including the periurethral zone, and can reach the urethra and even the bladder. The development of a UTI depends on the balance of several factors, including the bacterial load inside the urinary tract and in the periurethral zone, local defense mechanisms, and bacterial virulence [4].

UTIs are significantly more frequent in women than in men [2]. Acute cystitis symptoms develop quickly and include dysuria, increased urinary frequency, urinary urgency, and/or suprapubic pain. When a woman presents these symptoms alone or combined, the probability of cystitis is 50 and 90%, respectively [5]. Moreover, approximately 20–35% of women with a first epi-

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sode of cystitis will present with a recurrence during the following 6 months [6–8], with a majority showing symptoms in the first 2 months [9]. Most recurrences are reinfections from extraurinary sites such as the rectum [9].

Antibiotics are the mainstream therapy for UTI management. However, bacterial resistance to antimicrobials is steadily increasing at an alarming rate [10]. Resistance in Gram-negative uropathogens is an important health concern and the prevalence of *Enterobacteriaceae* resistant to betalactamics, fluoroquinolones, aminoglycosides and sulphonamides, including *E. coli* resistances [11], is rising rapidly [12]. According to a European study of women with acute uncomplicated cystitis, *E. coli* resistance, particularly to ciprofloxacin and trimethoprim, has significantly increased [13]. The challenge presented by this bacterial resistance calls for the reasonable use of antibiotics [14], and also new non-drug therapies for UTI treatment and prevention [11].

A new medical device (MD) has been approved for the control and prevention of UTIs: a capsule that consists mainly of a cross-linked protein, which also includes hibiscus and propolis (MD capsule). We present the results of a clinical trial conducted among women with uncomplicated acute cystitis treated with ciprofloxacin and the new MD or a placebo. The main objective was to assess the efficacy of the MD capsules compared with the placebo in the prevention of cystitis recurrence. The secondary objective was to verify whether the capsules associated with ciprofloxacin changed the symptomatic evolution of acute cystitis during the first 20 days after antibiotic therapy onset, that is, to assess their potential to improve acute symptoms of cystitis.

Methods

Patients

Patients were included in the study if they were Caucasian women aged ≥18 who presented with acute cystitis symptoms and had a clean-catch midstream urine culture with a ciprofloxacin-susceptible bacterial isolate (>10^3 CFU/ml). The study protocol was initially intended for patients of both sexes; however, due to the different pathophysiology of UTIs in men and women, only female patients were included.

Exclusion criteria included fever (defined as an axillary temperature >37°C or >98.6°F), pregnancy, breastfeeding, known urinary tract disorder and/or any known prior diagnosis of any relevant disease (heart, lung, kidney, liver and/or blood disease).

The study (EudraCT identifier 2012-000938-19) was approved by an independent Ethics Committee and developed according to the Declaration of Helsinki. All participants were required to sign an informed consent form before entering the study.

Study Design

A prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial was performed in Italy between October 2012 and May 2014.

In the initial assessment, patients with symptoms of acute cystitis were recruited and a urine sample was collected. Based on a total randomization procedure, patients were assigned to 1 of 2 treatment arms: ciprofloxacin 500 mg/day and 2 MD capsules/day, or ciprofloxacin 500 mg/day and matched placebo for 5 days. Each MD capsule contained 125 mg of cross-linked (reticulated) protein, 100 mg of dried *Hibiscus sabdariffa* calyx extract and 100 mg of propolis. After this period, patients were treated with 1 MD capsule/day or matched placebo for a further 15 days. Controls were performed on days 3, 5, and 20. Urine culture was assessed at day 20 and patients with a ciprofloxacin-susceptible isolate were included in the study.

Participants received 2 additional cycles of 1 MD capsule/day or matched placebo for 2 weeks at months 1 and 2 after initial treatment. Overall, this scheme corresponds to the posology of MD capsules for UTI treatment and recurrence prevention, according to the most likely time for recurrence [9]. Control visits were performed after 1, 2, 3 and 6 months. If patients presented with symptomatic cystitis, they were treated with an antibiotic and a further cycle of 2 MD capsules/day or matched placebo for 5 days.

Patients completed a daily micturition diary from the onset of the investigational treatment for 6 months, until the end of the study visit.

Endpoints and Assessments

The primary endpoint was the percentage of symptomatic cystitis recurrences over 6 months. Secondary endpoints were the number of micturitions as registered in the diary, and the dysuria based on a quantitative scale (0: no dysuria; 1: mild; 2: moderate; 3: severe).

Vital signs (axillary temperature, blood pressure (BP), and heart rate (HR)), physical examination and standard laboratory tests were used to assess safety.

Statistical Analysis

Descriptive analysis included the estimation of absolute and relative frequencies for qualitative variables as well as mean and standard deviation for quantitative variables. This quantitative variable hypothesis test was based on Student's t test. For recurrence analysis, Mantel–Haenszel test (log-rank test) was used; all patients that completed the follow-up were included in this analysis, thus observing the intention-to-treat principle. A p value <0.05 was considered to indicate statistical significance.

Safety assessments were based on the safety analysis population, defined as patients receiving one or more doses of study medication in a double-blind design and for whom some follow-up data was available.

A desired reduction from 35 to 5% of cystitis recurrence risk during the first 6 months was postulated. For an alpha risk of 5%, a power of 80% and a relationship of 1 between experimental and control groups, 44 patients per group were necessary according to the estimation using the corrected normal method. Assuming a drop-out rate of 20% after randomization, 108 patients had to be recruited.

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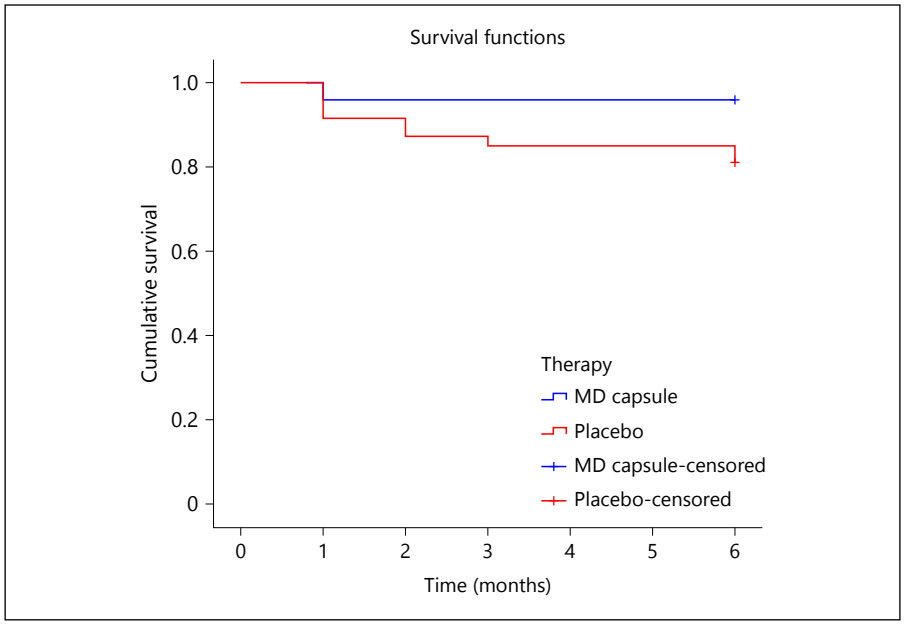

Fig. 1. Recurrence of acute uncomplicated cystitis in women treated with a new MD or placebo.

Table 1. Baseline characteristics of analysis population

Baseline characteristics	MD capsules (n = 43), mean ± SD	Placebo (n = 35), mean ± SD
Age, years	26.86±6.88	27.54±10.17
Weight, kg	61.05±6.25	60.46±7.18
Height, cm	166.42±4.85	163.29±5.42
BMI, kg/m^2	22.04±2.08	22.63±2.37
Temperature, °C	36.62±0.22	36.58±0.24
Systolic BP, mmHg	125.26±7.46	126.20±6.45
Diastolic BP, mmHg	73.42±6.18	73.20±5.72
HR, bpm	68.00±5.75	67.57±5.66

BMI = Body mass index; bpm = beats per minute.

Results

From the 102 patients recruited initially, 24 were excluded because no ciprofloxacin-sensitive isolates were detected in their urine cultures. Baseline characteristics of the 78 patients are shown in table 1.

Efficacy

No recurrence was observed after the first month of follow-up in the MD-treated group (fig. 1). After 6 months, symptomatic recurrence among patients treated with MD capsules was reduced by 19.4% compared with the placebo group (95% CI 11.25–27.55; p = 0.015).

The number of micturitions among patients treated with MD capsules was statistically and significantly reduced compared to that in the placebo group on days 3 and 20 (table 2). In addition, dysuria scores improved after 20 days of therapy in both groups. However, no statistically significant differences between the groups were observed (p > 0.05; table 3).

Safety

Diastolic BP and HR did not change throughout the study in either group (table 4). Although systolic BP was significantly higher in the placebo group, this difference was not considered clinically relevant or related to the study medication. Safety assessments based on physical examination and standard laboratory tests were within the expected range. No severe adverse events were observed.

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Table 2. Changes in the number of micturitions per 24 h

Number of micturitions	MD capsules (n = 43), mean ± SD	Placebo (n = 35), mean ± SD	Mean difference (95% CI)	p value
Baseline	9.56±1.74	8.94±1.75	0.615 (–0.174 to 1.405)	0.125
Change on day 3	–1.23±1.07	–0.71±0.89	–0.52 (–0.97 to –0.07)	0.025
Change on day 5	–2.33±1.38	–1.86±1.33	–0.47 (–1.08 to –0.15)	0.133
Change on day 20	–3.37±1.59	–2.57±1.60	–0.80 (–1.52 to –0.08)	0.030

Table 3. Changes in dysuria

Dysuria score	MD capsules (n = 43), mean ± SD	Placebo (n = 35), mean ± SD	Mean difference (95% CI)	p value
Baseline	2.14±0.77	2.00±0.80	0.14 (–0.22 to 0.50)	0.439
Change on day 3	–0.72±0.77	–0.49±0.51	–0.24 (–0.54 to 0.07)	0.123
Change on day 5	–1.44±0.88	–1.11±0.93	–0.33 (–0.74 to 0.08)	0.116
Change on day 20	–1.77±0.87	–1.49±1.01	–0.28 (–0.71 to 0.14)	0.190

Table 4. Safety analysis: changes in BP and HR from baseline

Safety variables	MD capsules (n = 43), mean ± SD	Placebo (n = 35), mean ± SD	Mean difference (95% CI)	p value
Systolic BP, mmHg	–0.07±3.04	1.38±3.01	–1.44 (–2.85 to –0.03)	0.045
Diastolic BP, mmHg	0.19±3.48	–0.75±3.19	0.94 (–0.63 to 2.50)	0.237
HR, bpm	–0.67±3.14	0.34±3.39	–1.02 (–2.53 to 0.49)	0.183

bpm = Beats per minute.

Discussion

Results of a prior study showed that MD capsules improved UTI symptoms and reduced the need for antibiotic therapy compared with a placebo [15]. In our study, the administration of MD capsules together with antibiotic therapy improved the control of acute cystitis symptoms, with a statistically significant reduction in the number of daily micturitions compared with the placebo. Besides symptom control, MD capsules reduced symptomatic recurrences, with a 19.4% difference compared with the placebo during the follow-up.

Although no specific measure is recommended after cystitis resolution, the high disease recurrence may support the use of some preventive measures. However, increasing bacterial resistance to antibiotics means that other therapies for UTI control and prevention are of special interest [9, 11]. The preventive effect of MD capsules may be due to the barrier effect created by its components in the intestine, thus reducing the contact between uropathogenic bacteria and epithelial mucosa and, therefore, diminishing bacteria proliferation and load. There could also be an ancillary effect on the vesical environment that impairs bacteria survival and development.

Even though many UTIs are caused by bacteria of intestinal origin, most measures for preventing recurrent cystitis do not act at this level. Saprophyte intestinal flora can be modified only by antibiotic therapy carried out for several months. However, antibiotic therapy can cause resistance and therapy intolerance [8]. Additionally, continuous antibiotic prophylaxis can be associated with adverse events [16]. The mechanical effect of the cross-linked protein reduces bacterial adhesion and proliferation inside the intestine. Accordingly, enterobacteria migration to the urogenital area, as well as any subse-

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quent UTI, can be prevented. In fact, similar products are beginning to be used for the management of acute gastroenteritis because they reduce intestinal proliferation of enterobacteria including *E. coli* [17].

Moreover, *H. sabdariffa* could decrease urine pH in animal experimentation [18] and urine acidification has been related to treatment and prevention of UTI [19].

H. sabdariffa has been found to have a mild lowering BP effect in hypertensive patients [20]. However, according to the study inclusion criteria, none of our patients had hypertension or hypotension. Furthermore, the increase in systolic BP in placebo group was not clinically significant. With the *H. sabdariffa* dose used in our study, BP did not decrease and HR did not increase.

Furthermore, a potential limitation of our study is that we focused on urinary symptoms and did not assess the potential intestinal effects of MD capsules.

Additional clinical trials are needed to assess the effect of each component of MD capsules and compare their results with a placebo and with the capsule itself. However, this study showed that MD capsules are better than the placebo at reducing the risk of a recurrence of uncomplicated acute cystitis in women. Furthermore, when MD capsules are administered together with antibiotic therapy, they improve symptom control with a lower number of micturitions compared with the placebo.

We conclude that MD capsules can help prevent recurrences of uncomplicated cystitis as well as reduce antibiotic use in UTI management in women.

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