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Efficacy and Safety of a Medical Device versus Placebo in the Early Treatment of Patients with Symptoms of Urinary Tract Infection: A Randomized Controlled Trial

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Abstract

Background: The objective of the study was to analyze the efficacy and safety of a medical device containing reticulated gelatin with hibiscus and propolis (RGHP) in the early treatment of patients with symptoms of urinary tract infection (UTI).

Methods: A double-blind, placebo-controlled trial was carried out in 60 patients who were randomized (1:1) to RGHP or placebo twice daily for 5 days. Follow-up was 11 days.

Results: The risk ratio of patients who needed antibiotic treatment was lower in the RGHP group (RR, 0.3; 95% CI, 0.09 to 0.98). RGHP provided greater symptom relief than placebo (mean adjusted change in the global symptom score from baseline: -5.27 vs. 0.40; p<0.001). Adverse events were reported by 6.67% and 3.33% of patients (RGHP and placebo, respectively, p=0.5).

Conclusions: RGHP was more effective than placebo in improving UTI symptoms and reduced the need for rescue antibiotic treatment.

Keywords: Cystitis; Urinary tract infection

Abbreviations

UTI: Urinary Tract Infections; RR: Risk Ratio; CI: Confidence Interval; RGHP: Reticulated Gelatin with Hibiscus and Propolis

Background

Urinary tract infection (UTI) is one of the most prevalent infectious diseases and therefore a widespread problem. During their lifetime, between 25% and 50% of women experience a UTI [1], which results in elevated morbidity, multiple antibiotic treatments, and increased costs [2]. In addition, 12% have recurrent UTI [3], which is defined as at least 2 UTIs in 6 months or 3 UTIs in a year. Most recurrences are believed to be reinfections from bacteria originating outside the urinary tract (e.g., in the intestine).

The main pathogen involved in these infections, *Escherichia coli*, has recently acquired resistance mechanisms against β-lactams and fluoroquinolones [4,5]. The unremitting emergence of multidrug-resistant bacteria highlights the need for alternative therapeutic options.

RGHP has been approved in the European Union as a class III medical device for the control and prevention of UTI. It contains a gelatin-reticulated complex, propolis, and *Hibiscus sabdariffa*. After ingestion, the gelatin-reticulated complex stratifies onto the intestinal mucosa to form a protective biofilm, which reduces adhesion and proliferation of uropathogens in the intestinal mucosa. This effect might reduce shedding to locations outside the intestine and thus prevent colonization of the urinary tract. Oral intake of propolis and *Hibiscus sabdariffa* can decrease urinary pH [6]. Infected urine contains large amounts of nitrite, and acidification of nitrite results in the formation of nitric oxide (NO), which has antimicrobial properties [7,8].

The objectives of this study were to compare the safety and efficacy profile of RGHP with that of placebo in improving symptoms and reducing the need for antibiotics in patients with UTI symptoms.

Methods

Study design and patient selection

A double-blind, placebo-controlled trial was carried out in Romania between May and June 2013. All procedures complied with the good clinical practice guidelines of the European Union and the principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Romanian Ministry of Health (Medical Device Department) and an independent ethics committee. The trial was registered with EudraCT (number 2014-000390-40) and was funded by Novintethical Pharma. All patients provided written informed consent to participate in the study.

Inclusion criteria were age ≥ 18 years, 1 or more symptoms of UTI (dysuria, urgency, suprapubic pain and/or urine organoleptic changes),

onset of symptoms <72 hours prior to study entry and positive dipstick urine test result (leukocyte esterase or nitrates).

Exclusion criteria were pregnancy, lactation, temperature ≥ 37.5°C, low back pain, treatment with antibiotics within 48 hours prior to study entry, known structural and/or functional abnormality of the urinary tract and impaired immunity secondary to chemotherapy, oral corticosteroids or human immunodeficiency virus (HIV) infection. Although HIV-infected patients receiving appropriate treatment can be considered immunocompetent, we did not include them in the study. Given the lack of specific data on immune response in the initial assessment, we preferred to consider it an exclusion criterion in order to avoid bias.

Patients visited the clinic at screening. Symptoms of UTI (dysuria, urgency, suprapubic pain and urine organoleptic changes) were measured on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe). Baseline symptoms were recorded, and patients received instructions on how to self-administer a questionnaire about daily symptoms and adverse events during treatment. Consecutive eligible patients were assigned a sequential run-in number and randomized (1:1) to RGHP or placebo twice daily for 5 days. RGHP took the form of hard capsules containing 125 mg of a gelatin-reticulated complex, 100 mg of propolis and 100 mg of dry extract of the calyces of *Hibiscus sabdariffa*. Placebo capsules were identical in appearance and were blistered and boxed in identical packages to maintain blinding for participants. Appropriate care was exercised in the handling of RGHP and placebo capsules. The placebo capsules contained mono- and diglycerides of fatty acids, maltodextrin, cornstarch and microcrystalline cellulose. Treatment was discontinued if symptoms worsened and/or severe adverse events developed. Diaries (symptoms and adverse events) were assessed 1 day after completion of treatment (day 6). Urine culture was ordered for patients who continued to experience UTI symptoms and antibiotics were prescribed. Six days after completion of treatment (day 11), patients were interviewed by telephone to investigate post-treatment adverse events.

Safety and efficacy assessment

The primary efficacy endpoint was the need for rescue treatment with antibiotics. Secondary measures included change in symptoms of UTI from baseline to end of treatment.

For the safety assessment, patient-reported adverse events were recorded according to guidelines on medical devices (MEDDEV 2.7/3). An adverse event was defined as any undesirable experience starting and/or worsening from the first dose of study medication until 6 days after the last dose. An adverse event was considered unrelated to treatment if there was no temporal relationship between administration and the event.

Statistical analyses

Symptoms of acute cystitis appear quickly and include dysuria, frequency, urgency and/or suprapubic pain. The probability of cystitis is greater than 90% in a patient who has those symptoms. The objective was to demonstrate a 50% reduction in the number of symptomatic patients in the RGHP group (5% α risk, 85% power). It was estimated that 27 evaluable patients per treatment group were required. In order to randomise 54 patients, planned enrollment was for 60, assuming a 10% dropout rate.

The mean and the standard deviation were used for the descriptive analysis of the quantitative variables. Absolute frequencies were used for the qualitative variables. Quantitative variables were analysed using the t test if they followed a normal distribution and the Mann-Whitney test if they did not. Statistical significance was set at <0.05. The analysis was performed using SPSS statistical package version 19 for Windows (IBM Corp, USA).

Results

Sixty patients were enrolled and randomised (30 per treatment group). Table 1 specifies the baseline characteristics of the patients. All patients completed the follow-up.

Variable	RGHP (n=30)	Placebo (n=30)
Age	51.27 (18.04)	59.37 (13.05)
Gender, n (%)		
Female	26 (86.7)	24 (80)
Male	4 (13.3)	6 (20)
Ethnicity, n (%)		
Caucasian	30 (100)	29 (96.7)
Oriental	0	1 (3.3)
Dysuria	2.23 (0.77)	1.87 (0.51)
Urgency	1.93 (0.79)	1.67 (0.99)
Suprapubic pain	1.43 (0.97)	1.00 (1.08)
Organoleptic changes	1.37 (1.10)	1.10 (1.06)

Table 1: Patient characteristics at baseline. All values are given as mean (standard deviation) unless otherwise indicated.

Efficacy

For the primary efficacy end point, the risk ratio (RR) of patients who needed antibiotic treatment was significantly lower in the RGHP group (RR, 0.3; 95% CI, 0.09 to 0.98). During the study, 3 of 30 patients (10%) in the RGHP group and 10 of 30 (33.3%) in the placebo group required antibiotic treatment (p=0.028).

RGHP was superior to placebo in terms of clinical course, which was assessed based on the mean adjusted change scores for dysuria, urgency, suprapubic pain and organoleptic urine changes (Figure 1). After completion of treatment, we recorded an improvement in all symptoms in the RGHP group (Table 2).

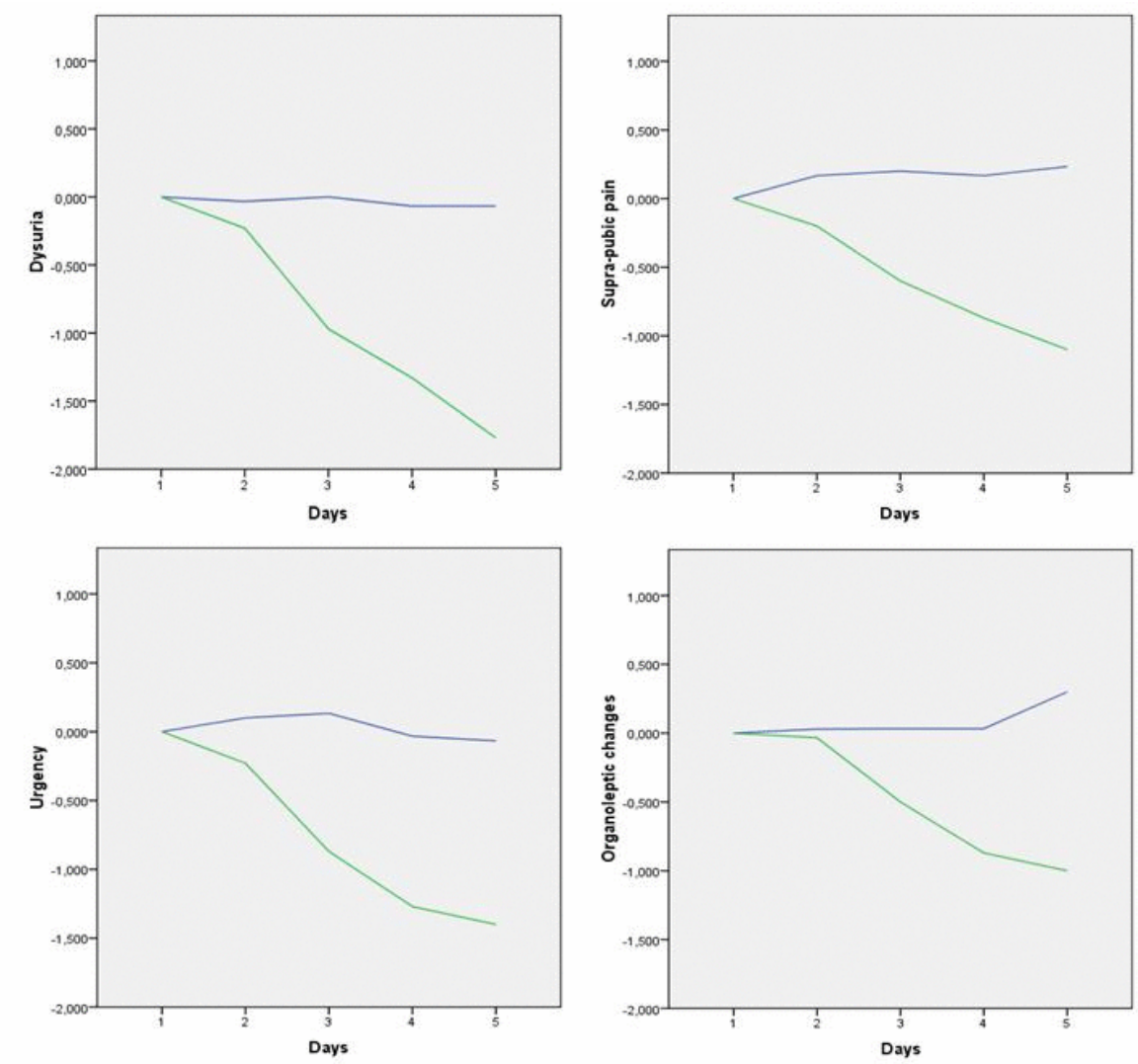

Figure 1: Progress of symptoms. Mean adjusted change in symptom scores from baseline. Treatment groups: RGHP in green, placebo in blue.

Variable	RGHP*	Placebo*	Treatment difference	P#
Dysuria	-1.77 (0.86)	-0.07 (1.14)	-1.70 (95% CI -2.22 to -1.18)	<0.001
Urgency	-1.40 (1.07)	-0.07 (1.08)	-1.33 (95% CI -1.89 to -0.78)	<0.001
Suprapubic pain	-1.10 (0.92)	0.23 (1.07)	-1.33 (95% CI -1.85 to -0.82)	<0.01
Organoleptic changes	-1.00 (1.20)	0.30 (0.92)	-1.30 (95% CI -1.85 to -0.75)	<0.001
Global symptom	-5.27 (3.30)	0.40 (3.51)	-5.67 (95% CI -7.43 to -3.91)	<0.001

Table 2: Mean adjusted change in symptom scores from baseline to end of treatment. *Mean (standard deviation). #t test.

Safety

Of the 30 patients in the RGHP group, one experienced diarrhoea and another had abdominal pain. Diarrhoea was reported by 1 patient in the placebo group. Therefore, adverse events were reported by 2 of 30 patients (6.67%) in the RGHP group and 1 of 30 patients (3.33%) in the placebo group (p=0.5). The adverse events recorded were of mild intensity and were not related to treatment.

Discussion

RGHP is a new class III medical device that has been approved in the European Union for the control and prevention of UTI. It contains a gelatin-reticulated complex, propolis, and a dry extract of the calyces of *Hibiscus sabdariffa*.

The gelatin included in the medical device is a reticulated complex of proteins and vegetable polysaccharides in which covalent links improve viscoelastic properties. Similar products reduce the growth of various pathogens, such as *Bacteroides fragilis*, *Clostridium perfringens*, *Escherichia coli*, *Enterobacter cloacae*, *Salmonella typhimurium*, *Helicobacter pylori* and *Listeria monocytogenes* [9]. In many European countries, these products are being marketed for the treatment of acute gastroenteritis [10]. Once ingested, the gelatin-reticulated complex stratifies onto the intestinal mucosa to form a protective biofilm that enables nutrients to be absorbed [11]. The gelatin film reduces the adhesion and the proliferation of uropathogens on the intestinal mucosa. This effect might reduce shedding to locations outside the intestine and thus prevent colonization of the vaginal mucosa and urinary tract. Unpublished preliminary results from a study performed in a rat model showed that RGHP was able to decrease counts of *Escherichia coli* in the intestine by 28%. Although 90% of UTI are produced by bacteria of intestinal origin, most treatments for recurrent cystitis do not affect this reservoir. Only low-dose, continuous antimicrobial prophylaxis regimens have been shown to eliminate intestinal pathogens. Increased antibiotic resistance is one of the principal problems associated with this approach, thus highlighting the need for alternative strategies. RGHP is the first product with the potential to block colonization by bacteria of intestinal origin.

In addition to the gelatin-reticulated complex, RGHP contains propolis and *Hibiscus sabdariffa*. Oral intake of propolis and *Hibiscus sabdariffa* can decrease urinary pH [6]. Infected urine contains large amounts of nitrite, and acidification of nitrite results in the formation of nitric oxide, which possesses antimicrobial properties [7,8]. Those mechanisms might explain the potential effectiveness of propolis and *Hibiscus sabdariffa* in the control of UTI. In a study with a 6-month follow-up, *Hibiscus sabdariffa* extract reduced the incidence of recurrent cystitis in women. Over a 24-week period, the incidence of UTI decreased in women taking hibiscus extract daily (77% vs. 20% for placebo group) [12]. We did not study the potential effects of decreased pH on each of these components. In addition, data on differences in the results of urine cultures between groups at the end of the trial were not collected. These limitations of our trial should be evaluated in future studies.

The present study compared the safety and efficacy profile of RGHP with that of placebo in the initial treatment of symptoms associated with uncomplicated UTI. The device can be taken once the first urinary symptoms appear, with the aim of reducing the proliferation of infectious pathogens. RGHP could be an early non-antibiotic alternative for patients before they consult their physicians. The principal limitation of our study is the short follow-up period. Since UTI can recur, follow-up periods in future studies may need to cover much longer periods in order to properly assess the natural course of the disease.

The properties of RGHP make it potentially useful as an adjuvant measure along with antibiotics in the treatment of uncomplicated UTI. It would be interesting to determine whether RGHP administered as adjuvant therapy for cystitis reduces the frequency of symptoms and/or of recurrence of the condition.

Recurrent cystitis is common among young and healthy women [13]. Foxman et al. [14] found that 20.9% of women with an index UTI had at least 1 symptomatic recurrence during the first 6 months [14]. Recurrence is most likely between 30 and 60 days after completion of treatment [15]. This incidence of reinfection during the initial months could justify the use of prophylactic strategies. Increasing antimicrobial resistance has stimulated interest in non-antibiotic prophylaxis of recurrent UTI. Several randomized controlled trials confirm the effectiveness of the oral immunostimulant OM-89, vaginal estrogens and proanthocyanidins [16]. Further studies are needed to determine whether RGHP is suitable for preventing the recurrence of UTI.

Conclusions

RGHP is a safe treatment that proved to be more effective than placebo in improving UTI symptoms and reducing the need for rescue treatment with antibiotics. It could be an early, non-antibiotic therapeutic measure for patients with symptoms of cystitis. Future studies with larger samples and longer follow-up are needed to analyze the role of RGHP as an adjuvant to antibiotic treatment and/or as a prophylactic measure to reduce the incidence of recurrent cystitis.

Trial Registration

EudraCT (number 2014-000390-40).

Conflict of Interest

Alejandro García-Larrosa has acted as a consultant for Novintethical Pharma. Octavian Alexe has no competing interests to disclose.

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