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Efficacy and safety of *Lactobacillus plantarum* P 17630 strain soft vaginal capsule in vaginal candidiasis: a randomized non-inferiority clinical trial

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Abstract. – OBJECTIVE: To investigate the non-inferiority of efficacy and tolerability of *Lactobacillus plantarum* P 17630 soft vaginal capsules compared to the antifungal therapy with miconazole nitrate 400 mg soft vaginal capsules in patients with symptomatic vulvovaginal infection due to *Candida*.

PATIENTS AND METHODS: Adult women with vulvovaginal candidiasis were randomized to either *L. plantarum* P17630 100,000,000 CFU soft vaginal capsules by vaginal route each day for 3 or 6 consecutive days or miconazole nitrate 400 mg soft vaginal capsule. Visual Analog Scale (VAS) scores for vaginitis symptoms were used, and vaginal fluid interleukin 6 (IL6) was dosed. The study was registered in EudraCT database (code LPP17630-C-018; number: 2018-003095-12).

RESULTS: 200 patients were included in the study. The mean VAS scores for vaginitis symptoms were progressively reduced in both treatment groups at each visit, without significant difference between groups ($p>0.05$ for each symptom, at each time point). The efficacy of *L. plantarum* and the reference medicinal product was maintained at follow-up (day 21). The mean concentration of IL-6 decreased from visit 1 to visit 3 in both groups without a significant difference ($p>0.05$). No adverse events were reported.

CONCLUSIONS: *L. plantarum* P17630 100,000,000 CFU soft vaginal capsules are effective and safe for treating vaginal candidiasis without the concomitant use of an antifungal product, which rules out the risk of antimicrobic resistance. The long-term effect on vaginal microflora may add the possibility of reducing the risk of recurrences.

Key Words:
Vulvovaginal candidiasis, *L. plantarum* P 17630, Soft vaginal capsules.

Introduction

The vaginal microbiota plays a crucial role in preserving health and warding off infections. When there is a disturbance in the vaginal microbial community, referred to as vaginal dysbiosis, it is often associated with an elevated susceptibility to vaginal infections, including vulvovaginal candidiasis (VVC)[1]. Vaginal candidiasis is a highly prevalent condition, affecting 70-75% of women at any age during their lifetime[2]. *Candida albicans*, a fungal pathogen, poses a significant threat to human health, giving rise to a range of infections. This pathogen is identified in 85-95% of cases, highlighting its widespread association with the occurrence of vaginal candidiasis. Candidiasis is often uncomplicated and can resolve quickly, but 9% of patients with VVC experience recurrence, defined as four or more repeated episodes of the infection within a year[3,4]. *Candida* species are usually found in the lower genital tract of 10-20% of healthy women of childbearing age. The evolution to symptomatic infection is due to host factors, such as susceptibility and inflammatory responses and/or the imbalance of vaginal microbiota[5]. Epithelial cells play a role in the inflammatory process by generating cytokines and chemokines. This suggests that epithelial cells could potentially contribute to the regulation of *Candida* infections by engaging in an inflammatory response mediated by various substances, including interleukin-6 (IL-6), IL-8, and tumor necrosis factor alpha (TNF-α)[6]. The vaginal microbiota of healthy women is dominat-

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ed by *Lactobacilli*, non-pathogenic living microorganisms which exert significant health-promoting effects on the host[7]. *Lactobacilli* are depleted during infectious vaginosis, suggesting their pivotal role in the anti-infection defense of urogenital mucosa. The mechanisms of the anti-infective function of *Lactobacilli* are not fully understood, but several hypotheses have been presented based on different observations[8,9]. *Lactobacilli* produce several antimicrobial compounds (e.g., hydrogen peroxide, lactic acid and create a physical barrier against pathogen adhesion in the vaginal epithelium, with a protection activity against diseases such as recurrent urinary infections, bacterial vaginosis (BV), and VVC[7]. Current treatment regimens, predominantly relying on antifungal agents, such as azoles (e.g., fluconazole, clotrimazole), demonstrate effectiveness in managing candidiasis[10]. However, antifungal resistance in *Candida* species, especially in the context of VVC, is a growing concern in healthcare. The emergence of resistance is on the rise, attributed to factors like overuse, misuse, and the prevalence of non-albicans species[10,11]. Moreover, the impact of these medications on the local microbiota is not well understood. Notably, fungicidal compounds do not contribute to the restoration of a healthy vaginal microflora and may potentially predispose susceptible women to recurrences and/or reinfections[12]. *Lactobacillus plantarum* P 17630 is a strain known to be able to colonize the vagina[13], with a particular ability to adhere to vaginal epithelium and to compete against *C. albicans*[14,15]; moreover, *L. plantarum* P17630 can survive in a broad range of temperature and pH and is one of the few *Lactobacillus* strains that are resistant to many commonly used antibiotics, including vancomycin and azoles; biofilm production was also noted[16]. Live biotherapeutic products (medicinal products containing live microorganisms) represent a strategy to restore local microbiota and treat an infection without the risk of resistance related to antibiotics and antimycotics[17]. The administration of oral or topical *L. plantarum* P 17630, either alone or in addition to an antifungal product, was found to improve vagina colonization with lactic acid bacteria, suggesting a favorable role in treating candidiasis and preventing recurrences[4,18]. The concomitant administration of soft capsule *L. plantarum* P 17630 and one-dose fluconazole reduced the incidence of candidiasis recurrences by 72% compared to fluconazole alone[19]. Moreover, as *Candida* isolates induced host cells to release proinflammatory cytokines, including IL-6[6,20], a decrease in their levels, along with other factors, may suggest *Candida* eradication. Indeed, gene expression analysis in epithelial cells revealed that live *C. albicans* increased the expression of the IL-6 gene. In contrast, exposure to heat-killed *C. albicans* did not induce IL-6 release, indicating that only live *C. albicans* has the ability to upregulate both IL-6 expression and secretion[21,22]. Moreover, pretreatment of HeLa cells with vaginal *Lactobacillus plantarum* and *Lactobacillus fermentum* isolated from healthy Cuban women reduced the production of proinflammatory cytokines IL-1β, IL-6, and IL-8 when challenged with *C. albicans*[23,24]. This study was designed to investigate the non-inferiority of efficacy and tolerability, assessed by clinical evaluation and by IL-6 dosing, of *L. plantarum* P 17630 100,000,000 CFU soft vaginal capsules compared to the antifungal therapy with miconazole nitrate 400 mg soft vaginal capsules in patients with clinically symptomatic vulvovaginal infection due to *Candida*.

Patients and Methods

A randomized, investigator-blinded, active-controlled, multicenter, two-parallel-group study was designed and carried out between September 2019 and February 2020.

The study was approved by the Bulgarian Drug Agency (protocol Ref. No. КИ-109-2-0045/26-07-2019). The study was conducted according to the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the Good Clinical Practices, and the clinical principles of the Declaration of Helsinki (Brazil, October 2013). All enrolled patients released written informed consent. The study was registered in the European Union Drug Regulating Authorities Clinical Trial Database (code LPP17630-C-018; EudraCT number: 2018-003095-12).

Subjects

Premenopausal women between 18 and 45 years of age diagnosed with vulvovaginal candidiasis based on symptoms (pruritus, discharge, pain, dryness) and negative results for bacterial vulvovaginitis (assessed by the Gyno-Canestest® kit, Bayer AG, Leverkusen, Germany) were enrolled.

The main exclusion criteria were menstruating at the baseline visit, primary or secondary immunodeficiency, severe liver disease, history of

regional enteritis or ulcerative colitis, evidence of non-bacterial vulvovaginitis within the last 4 months, cervical neoplasia, history of hypersensitivity to study medications, use of topical or systemic antibiotics/antifungal drug within 2 weeks prior to the baseline, and use of intra-vaginal device or product within 48 hours prior to first dosing.

Study Treatments

Each patient was randomized to receive either *L. plantarum* P17630 100,000,000 CFU soft vaginal capsules [LJ LACTO, medicinal product licensed by the company Proge Farm S.r.l. – Novara, Italy], or miconazole nitrate 400 mg soft vaginal capsules (DAKTARIN®, Janssen Cilag Spa, Milan, Italy), by vaginal route each day, for 3 consecutive days starting from the evening of visit 1 (baseline). The therapy was stopped if complete recovery was ascertained at visit 2 (day 3) or continued for another 3 days (visit 3). The exact time of administration was reported in the patient's diary. No medications were allowed during the study periods. No sexual intercourse was allowed on days 0-7.

Study Plan

The primary objective was to evaluate the non-inferiority of the efficacy of *L. plantarum vs.* miconazole in patients with vaginal candidiasis based on the assessment of vaginal pruritus, discharge, pain, and dryness using a daily VAS scale. The secondary objective was to assess IL-6 concentration as a marker of inflammation and infection[18], evaluated by validated method of Enzyme-Linked Immunosorbent Assay (ELISA).

At baseline, investigators recorded vaginal symptoms and assigned the treatment starting the same day. On day 3 (visit 2), the patient was visited, and if healed, the treatment was stopped. She continued the treatment until visit 3 on day 6 if symptoms were still present. A follow-up visit (visit 4) was carried out on day 21. Symptom severity was evaluated on a VAS scale from 0 to 10, in which 0 was no symptoms, and 10 was severe. All adverse events occurring during the study were recorded. IL-6 concentration was measured in the vaginal fluid recovered at visits 1, 2, and 3.

Statistical Analysis

A sample size of 100 patients per treatment arm was calculated in order to have a significant statistical result with a clinical margin of 20% and to obtain a 90% power to demonstrate the non-inferiority of *L. plantarum* P 17630 *vs.* miconazole nitrate (α level, 5%; β level, 10%). Descriptive analyses were performed using point and confidence interval estimation. Inferential analysis was performed using a nonparametric unpaired test to compare the number of patients who stopped the treatment after 3 days and after 6 days. The VAS mean score values at baseline and visits 2, 3, and 4 were also evaluated. Treatment effects were assessed using an unpaired *t*-test, Mann-Whitney, and contingency Fisher's exact tests. The statistical significance was set at $p \leq 0.05$. All analyses were performed with IBM SPSS Statistics for Windows.

Results

Overall, 210 patients were screened, and 200 were enrolled and treated in four different clinical centers. The mean ± SD age of enrolled subjects was 33±6 years; their mean ± SD weight was 63±8 kg, and their mean ± SD height was 170±0.06 cm. No relevant data were recorded from medical histories. On day 1, 100 patients per group started the treatments.

Efficacy

The mean VAS scores for vaginitis symptoms were progressively reduced in both treatment groups at each visit, without significant difference between groups ($p > 0.05$ for each symptom, at each time point). The efficacy of *L. plantarum* P17630 and the reference medicinal product was maintained at follow-up (day 21), with similar VAS scores compared to the visit of the complete recovery (visit 2 of day 3 or visit 3 of day 6) in the overall population of the group (Table I).

At visit 2 (day 3), 20 patients on *L. plantarum* P17630 and 26 on miconazole were judged to have entirely recovered by the investigator. Two patients (one from the reference group and one from the test group) dropped out for personal reasons. The other 79 on *L. plantarum* P 17630 and 73 on miconazole continued the treatment for an additional 3 days. At follow-up, 99 patients on *L. plantarum* P 17630 and 97 (two patients failed to attend the visit) on miconazole were evaluated. No significant difference was found in the change of mean VAS scores for any symptom from baseline to visit 2 in patients considered healed and from baseline to visit 3 in those who continued the treatment for

Table I. Mean VAS scores ± SD for symptoms of candidiasis in the overall populations of the groups treated with *L. plantarum* and miconazole at each study visit.

Symptoms of vaginal candidiasis	Visit 1		Visit 2		Visit 3		Follow-up visit	
	L. plantarum P (n = 100)	Miconazole (n = 100)	*L. plantarum* P (n = 99)	Miconazole (n = 99)	*L. plantarum* P (n = 79)	Miconazole (n = 73)	*L. plantarum* P (n = 99)	Miconazole (n = 97)
Pruritus	5.84 ± 2	5.57 ± 3	2.84 ± 2	2.47 ± 2	0.93 ± 1	0.55 ± 1	0.61 ± 1	0.42 ± 1
Discharge	6.85 ± 2	6.91 ± 2	3.26 ± 2	3 ± 1	1.19 ± 1	0.92 ± 1	0.71 ± 0.8	0.58 ± 1
Pain	2.94 ± 3	2.91 ± 2	1.2 ± 1	0.87 ± 1	0.13 ± 0.3	0.08 ± 0.4	0.26 ± 0.9	0.07 ± 0.3
Dryness	3.46 ± 3	3.84 ± 3	1.23 ± 1	1.11 ± 1	0.24 ± 0.4	0.18 ± 0.5	0.22 ± 0.8	0.06 ± 0.2

Table II. Mean VAS scores ± SD for symptoms of vaginal candidiasis at visits 1 and 2 in patients treated with *L. plantarum* P 17630 or miconazole who stopped treatments on day 3.

Symptoms of vaginal candidiasis	Visit 1		Visit 2	
	L. plantarum P (n = 20)	Miconazole (n = 26)	*L. plantarum* P (n = 20)	Miconazole (n = 26)
Pruritus	5.85 ± 0.4	4.69 ± 3	0.45 ± 1	0.38 ± 1
Discharge	5.9 ± 2	6.27 ± 2	1 ± 2	0.92 ± 1
Pain	2.7 ± 3	2.15 ± 2	1.2 ± 1	0.15 ± 0.7
Dryness	3.6 ± 3	3.58 ± 3	0.25 ± 0.7	0.23 ± 0.8

Table III. Mean VAS scores for symptoms of vaginal candidiasis at visits 1 and 3 in patients treated with *L. plantarum* P 17630 or miconazole who continued treatments up to day 6.

Symptoms of vaginal candidiasis	Visit 1		Visit 3	
	L. plantarum P (n = 79)	Miconazole (n = 73)	*L. plantarum* P (n = 79)	Miconazole (n = 73)
Pruritus	5.89 ± 2	5.96 ± 2	0.87 ± 1	0.55 ± 1
Discharge	7.09 ± 2	7.15 ± 2	1.19 ± 1	0.79 ± 1
Pain	3.03 ± 3	3.22 ± 2	0.29 ± 0.6	0.04 ± 0.2
Dryness	3.46 ± 3	3.99 ± 3	0.39 ± 0.9	0.08 ± 0.2

6 days. The mean values are reported in Tables II and III.

The mean concentration of IL-6 decreased from visit 1 to visit 3 in both groups without a significant difference (p>0.05) between groups (Figure 1).

Safety

No severe or non-serious adverse or life-threatening events were reported by the patients or documented by the investigators throughout the study in both groups.

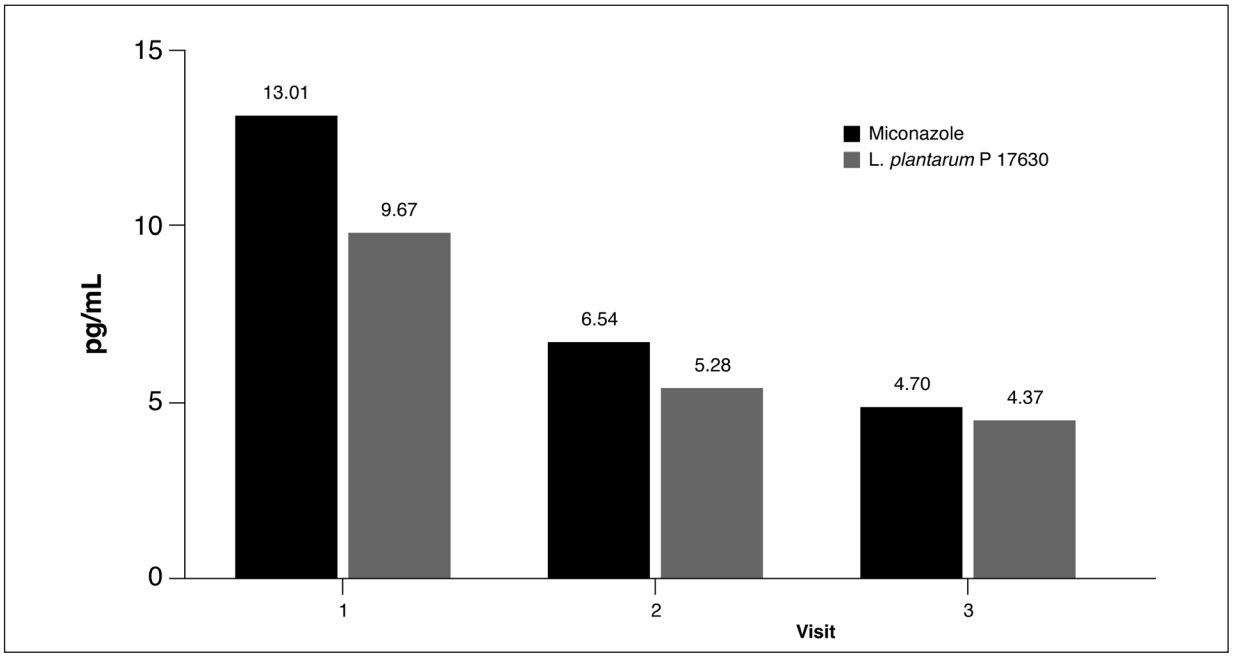

Figure 1. Mean ± standard deviation of IL-6 concentration in patients treated with *L. plantarum* P 17630 and with miconazole at baseline and after 3 and 6 days.

Discussion

This clinical study investigated the efficacy and safety of *L. plantarum* P17630 100,000,000 CFU soft vaginal capsules in women with vaginal candidiasis. It showed comparable effectiveness to the treatment involving miconazole soft vaginal capsules, which served as the reference medication. Moreover, the soft vaginal capsules containing *L. plantarum* P17630 at a concentration of 100,000,000 CFU were successful in addressing the four clinical indicators associated with vaginal candidiasis (itching, discharge, pain, and dryness) and in reducing IL-6 levels in the vaginal fluid. No adverse events were reported in either of the groups.

To our knowledge, this is the first published non-inferiority study of a medicinal product containing *Lactobacillus* compared to a conventional antimycotic medicinal product. These results suggest that topical *L. plantarum* P17630 alone is effective and safe for treating candidiasis. It may be used not only as an adjunctive treatment but as an alternative to antifungal drugs. This result may be of practical importance as treatment with a live biotherapeutic product has no risk of antimicrobial resistance[24]. It had previously been demonstrated that oral *L. plantarum* P17630 may improve vaginal colonization, suggesting that different administration strategies may concur to the prevention of recurrences[25]. Candidiasis has a high incidence and frequent recurrences and is related to repeated and prolonged exposure to conventional antifungal treatments, which makes resistance a heavy problem.

A previous study by Carriero et al[19] suggested that administration of *L. plantarum* P17630 may be continued, after a main course of treatment to restore the vaginal microflora, to prevent recurrences. As candidiasis has a high risk of recurrence due to the persistence of risk factors such as mucosa atrophy, metabolic diseases, and concomitant medications, the use of a product that may be used for prolonged periods without inducing resistance with a good safety profile, is of paramount importance, together with the possibility of restoring the physiological defense of the vagina environment. Our results may support the previous findings by Palacios et al[28].

Limitations

A limitation of this study was that candidiasis was diagnosed according to the current clinical practice based on clinical observation and bacteriological exclusion of bacterial infection, but no mycological test was carried out, either by microscopic observation or culture of vaginal fluid; the presence and the concentration of the proinflammatory cytokine interleukin-6 (IL-6), reported as released in response to *Candida albicans*, was evaluated[26].

Conclusions

L. plantarum P17630 100,000,000 CFU soft vaginal capsules are effective and safe for treating vaginal candidiasis without the concomitant use of an antifungal product, which rules out the risk of antimicrobic resistance. The long-term effect on vaginal microflora may add the possibility of reducing the risk of recurrences.

Conflict of Interest

CB and AB are employed in Proge Medica, a Company linked to Proge Farm. DS, LM, SB, DD have no conflicts of interest.

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Availability of Data and Material

All data are available from the corresponding author, upon reasonable request.

Authors' Contribution

Study conception and design: Daniele Savio, Antonella Bonetti; collection and interpretation of data: Daniele Savio, Stefan Bouzalov, Darina Davidova; statistical analysis: Daniele Savio; manuscript drafting: Antonella Bonetti, Chiara Bertarello, Lorenzo Morelli; approval to submit: all authors.

Ethics Approval

The study was approved by the Bulgarian Drug Agency (protocol Ref. No. КИ-109-2-0045/ 26-07-2019).

Informed Consent

Participants signed informed consent before being enrolled in the study.

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