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Efficacy and safety of oral administration of a product based on hydroxytyrosol as preventive therapy for recurrent vulvo-vaginal candidosis: a prospective observational pilot study

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Abstract. – OBJECTIVE: The aim of the study is to evaluate the efficacy and safety of hydroxytyrosol for the prevention of the vulvar vaginal candida infections recurrence.

PATIENTS AND METHODS: This study is a prospective observational pilot study. Eligible subjects were at least 18 years old, with at least 4 documented episodes of vulvovaginal candidiasis in the last 12 months. Patients were instructed to therapy (2 tabs daily for the first month and then 1 tab daily for 2 other months). Each capsule consists of hydroxytyrosol (HT) and other components: tea tree oil, tabebuia, juglans regia, and copper. Clinical and microbiological assessments took place at baseline and 12 weeks after. The impact on Quality of Life (QoL) was evaluated with the SF-36 and the Patient Global Impression of Improvement (PGI-I) after 3 months of treatment was calculated.

RESULTS: Sixty patients were enrolled in the study. In the last 1 year the mean number of previous infections was 5.83 ± 2.76. Forty-nine patients (83%) did not have candida episodes during 3 months of treatment. A significant reduction in clinical symptoms, vaginal signs, such as pruritus, burning and vulvar erythema (< 0.0001). The SF-36 showed a significant change (55.67±8.43 *vs*. 84.56±11.56, $p < 0.0001$) and the total success at PGI-I was reported in 54 patients (90%).

CONCLUSIONS: The HT-based product is effective and safe in preventing recurrent candida episodes and improves the quality of life and sexual function of treated women.

Key Words:
Infections, Sexually transmitted infection (STD), Benign disease of vulva and vagina, Recurrent vulvo-vaginal candidosis, Hydroxytyrosol, Prevention

Introduction

Fungal infection of vulvovaginal environment is the second most common cause of inflammation after bacterial vaginosis. The most common pathogen is *Candida albicans*, which is isolated in 85-90% of all cases[1]. An estimated 75% of women will have at least one episode of vulvovaginal candidosis (VCC) during their lifetime and 40-50% of these will experience further episodes[1]. Typical symptoms of VVC include pruritus, dyspareunia, internal and external dysuria, abnormal vaginal discharge, and erythematous vulva, but none of this is specific. Asymptomatic colonization with *Candida spp.* is also common. It can be found in one-third of women without any symptoms[2]. Recurrent VVC (RVVC) is defined as four episodes or more recurrent attacks of VVC within 1 year and it is one of the great challenges in clinical practice with a global annual incidence ranging of 1-2% of all women[3]. The pathogenesis of RVVC is poorly understood, and most women with RVVC have no apparent predisposing or underlying conditions. *C. glabrata* and other *nonalbicans C.* species are observed in 10-20% of women with RVVC[4]. Recurrent VVC may be caused by treatment-resistant *Candida*, species other than *C. albicans*, and has been associated with frequent antibiotic therapy, use of oral contraceptive pill, immunocompromised states such as human immunodeficiency virus (HIV) and hyperglycemia[5]. While current therapeutic approaches are effective in treating primary acute VVC, approximately 5-8% of US women in their

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reproductive age still encounter the problematic RVVC[6]. Guidelines suggest, for the uncomplicated VVC, the use of short-term therapy for 3 days with local azoles with the disappearance of symptoms after 2 or 3 days[7]. Treatment with azoles results in relief of symptoms and negative cultures in 80%-90% of patients who complete therapy. Complicated cases of VVC require prolonged treatment [7]. Moreover, is very important to provide maintenance therapy also for 6 months as the first line maintenance regimen. Furthermore, there is no important evidence about the long-term treatment of RVVC[8]. Above all, there is obviously an alteration of the vaginal microbiota when patients are treated too long[9]. The vaginal microbiota is characterized by different *Lactobacillus* and other microbial species[9]. It has long been suggested that the correct vaginal microbiota contributes to protection against microbial pathogens[10]. Recent data suggest that the association of Hydroxytyrosol (HT) with copper reduces the recurrence of RVVC without affecting the vaginal microbiota [11]. HT is an amphipathic phenol with a molecular weight of 154.16 g/mol and a phenylethyl-alcohol structure present in olive oil it has been described as an antioxidant with many biological activities. It is well known that both olive tree leave's extracts and pure HT have a powerful antimicrobial activity against some microorganisms such *Escherichia coli*, *Candida albicans*, *Clostridium perfringens, Streptococcus mutans*, or *Salmonella enterica*[12]. The aim of this study is to evaluate the efficacy and safety of HT as a preventive therapy in the recurrence of vulvar vaginal candida infections.

Patients and Methods

This study is a prospective observational pilot study on the efficacy and safety of HT for prevention of vulvovaginal candida infections. We enrolled patients between April 2016 and April 2017 in the Department of Surgery-Week Surgery, University of Rome "Campus Biomedico". Women who had history of recurrent VVC were invited to participate. Institutional Review Board approved this study. All data were evaluated from a urogynecological internal database. Eligible subjects were at least 18 years old, with at least 4 documented episodes of vulvovaginal candidiasis in the last 12 months. The severity score was based on the presence of objective symptoms (itching, irritation, and burning) and vulvovaginal signs (erythema, edema, and excoriation, or fissures). The severity of each sign or symptom was scored on a scale of 0 (absent or normal) to 3 (severe). The inclusion criteria and exclusion criteria are shown in Table I. Women with any sexually transmitted disease or genital skin disorder were also excluded. Patients were instructed to therapy (2 tabs daily for the first month and then 1 tab daily for 2 other months) s.r.l. Nutralabs (Serramazzoni, Modena, Italy). Each capsule consists of HT and other components: Tea Tree Oil, Tabebuia, Juglans Regia, Copper. Clinical and microbiological assessments took place at baseline and 12 weeks after the initial visit. Clinical symptoms, any adverse events (attributable to the treatment), physical vulvovaginal examination were assessed. At the start and at the end of the study, clinical symptoms (pruritus, burning and dyspareunia) and objective signs (vulvovaginal oedema and erythema and vaginal secretion) were evaluated. The primary endpoint was the number of VVC recurrences during the 3 months of treatment. A VVC episode was defined by significant symptoms (pruritus, dyspareunia, internal and external dysuria, abnormal vaginal discharge, and erythematous vulva) or positive vaginal culture. The secondary outcome was the variation of related vulvovaginal symptoms detected by clinical assessment and finally the impact on QoL evaluated with the SF-36 [13]. The Patient Global Impression of Improvement (PGI-I) after 3 months of treatment was calculated [14].

Table I. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion criteria
• Age between 18-80 years old • History of recurrent VVC • Negative vaginal culture at baseline	• Pregnancy or lactation • Allergy to the study medication • Use of antibacterial or antimycotic therapy (topical or systemic) in the previous 10 days • Sexually transmitted disease or genital skin disorder

Statistical Analysis

Statistical analysis was carried out with Wilcoxon matched pairs test for the continuous variables χ-square test for the frequency data. Quantitative data were expressed as mean ± SD (standard deviation) in tables. Student-*t* test and Mann-Whitney U test were used. Matched *t*-test was applied to determine the change in SF-36 values. Paired, independent *t*-tests and the Pearson's Chi-square test were used to determine the significance of differences before and after treatment. All analyses were conducted using the Statistical Package for the Social Sciences (SSPS Inc., Armonk, NY, USA, 22.0 for Mac). Significance was set at a *p*-value of < 0.05.

Results

Sixty patients were enrolled in the study. All 60 patients examined ended the proposed treatment and none was excluded until the last follow-up. The baseline demographic and clinical characteristics of patients are shown in Table II. In the last year the mean number of previous infections was 5.83 ± 2.76. Forty-nine patients (83%) did not have candida episodes during 3 months of treatment. Eleven women (17%) experienced at least one episode of recurrence during the 3-months treatment. During the 3 months of the study there was a significant reduction in clinical symptoms and vaginal signs, such as pruritus (1.09 ± 0.78 *vs*. 4.98 ± 1.22), burning (1.34 ± 0.76 *vs*. 5.54 ± 1.43) and vulvar erythema (0.98 ± 0.54 *vs*. 4.12 ± 1.39). The SF-36 has shown a statistically significant change (55.67 ± 8.43 *vs* 84.56 ± 11.56, $p <$ 0.0001) after 3 months of treatment, (Table III). The mean number of weekly intercourses has increased during the 12 weeks of treatment: 1.54 ± 1.13 *vs*. 2.32 ± 1.54 (p 0.002). No adverse effects and complications were reported. The PGI-I after 3 months of treatment reported by patients was: 51 patients felt very much better (85%), 3 much better (5%), 3 a little better (5%), 3 no improvement (5%). The total success (very much better + much better) was reported in 54 patients (90%) (Table III).

Discussion

The present pilot study is the first in literature to demonstrate the efficacy and safety of a product based on HT as preventive therapy for women affected by RVVC. The pathogenesis of RVVC is poorly understood due to various risk factors responsible for this disease. RVVC is a frequently problem worldwide, in fact 40-50% of women experienced recurrence with negative impacts on sexual life and consequently on quality of life [15,16]. Therapeutic management for RCCV is complex due to the complicated etiopathogenesis and due to increasing resistance to azole antifungals. Several treatment and prophylaxis regimens have been tested, but the recurrence rate during and after treatment has been shown to be yet high [17].

Over the past 10 years, fluconazole and itraconazole have been used extensively for chemoprophylaxis and treatment of systemic fungal infections because of their favorable oral bioavailability and safety profiles. However, *Candida species* are highly resistant to existing agents[18].

Table II. Demographic and clinical characteristics of 60 patients.

Variables	N	Variables	N
Age, y (mean ± SD)	39.75 ± 13.48	Smoke (%)	14 (23.3)
BMI (mean ± SD)	23.52 ± 5.43	Oral contraception (%)	18 (30)
Parity (range)	1 (0-3)	Diaphragm or IUD contraception (%)	3 (5)
Age of menarche	13.43 ± 1.61	Menopause (%)	15 (25)
Previous Pelvic Surgery (%)	8 (13.3)	HRT (%)	3 (12)
Sexual Activity (%)			
• 0-2 weekly (%)	40 (66.6)		
• 2-4 weekly (%)	15 (25)		
• more than 4 weekly (%)	5 (8.4)	Previous Infections in the last 1 year) (mean ± SD	5.83 ± 2.76
Food Habit			
• Mediterranean diet	60 (100)		
• Vegetarian diet	0 (0)		

Abbreviation: SD: Standard Deviation; n: number of patients; BMI: Body Mass Index; HRT: Hormonal Replacement Therapy.

Table III. SF-36 Comparison of (Last 1 year) and at 3-months FU and Patient impression of global improvement (PGI-I) after 6 months of treatment in 60 patients.

SF-36				PGI-I after 3 months	
Variables	Baseline (Last 1 year)*	3-months FU**	*p* value	Variables	N (%)
Burning (%)	5.54 ± 1.43	1.34 ± 0.76	< 0.0001	1: very much better (%)	51 (85)
Pruritus (%)	4.98 ± 1.22	1.09 ± 0.78	< 0.0001	2: much better (%)	3 (5)
Itching (%)	3.89 ± 1.87	1.07 ± 0.76	< 0.0001	3: a little better (%)	3 (5)
Vulvar erythema (%)	4.12 ± 1.39	0.98 ± 0.54	< 0.0001	4: no improvement (%)	3 (5)
Edema (%)	5.12 ± 2.08	0.73 ± 1.04	< 0.0001	5: a little worse (%)	0
Vaginal discharge (%)	4.97 ± 1.76	0.54 ± 0.62	< 0.0001	6: much worse (%)	0
Tenesmus (%)	3.17 ± 1.45	1.21 ± 0.74	< 0.0001	7: very much worse (%)	0
Vaginal dryness (%)	4.59 ± 2.11	1.47 ± 0.87	0.0006	Success (%)	54 (90)
Dyspareunia (%)	2.32 ± 1.21	0.71 ± 0.32	< 0.0001		
Antibiotics use (%)	4.15 ± 1.32	0.52 ± 1.03	0.0005		
SF-3655.67 ± 8.43	84.56 ± 11.56	< 0.0001			
Sexual Activity (mean ± SD)***	1.54 ± 1.13	2.32 ± 1.54	0.002		

Abbreviations: SF-36: the Short Form (36) Health Survey, n: number of patients. *Mean number of episodes in 60 patients in the last 1-year before treatment start. ** Mean number of episodes in 60 patients in the 3 months during treatment. ***Mean number of weekly intercourses.

An intrinsically reduced susceptibility to fluconazole has been also reported for *non*-albicans species of *Candida like C. glabrata*, *C. krusei*, and *C. lusitaniae*[19].

The mechanisms underlying development of antifungal resistance are complex and involve multiple pathways and genes[17].

Different molecules have been studied and are being tested: new triazoles, peptides such as lysozyme, lactoferrin, defensins, histatin, and cathelicidins, vaccines, anti-candida natural compounds, leukotriene receptor antagonist, probiotics and synergistic effects of plant extracts or their phytoconstituents with traditional agents[20,21]. Obviously all these new therapeutic strategies are still to be standardized and validated with more solid data to prove the efficacy in reducing infection recurrence.

In this study a significant reduction in candida episodes was demonstrated in the patients treated; in fact 83% of them had no recurrences during the 3 months of HT treatment regimen.

Moreover, hydroxytyrosol successfully regulated the reduction of RVVC and also the related symptomatology. Consequently, the absence of side effects, determined an excellent compliance to the therapy.

Patients with recurrent vaginal candidiasis are more likely to suffer from clinical depression, significantly less satisfied with life, poorer self-esteem, high stress levels, feelings of frustration, sexual dysfunction and dissatisfaction with life [22]. Therefore, finding a maintenance therapy that does not increase antibiotic resistance is the right way to follow in these patients.

Women have experienced a great improvement in quality of life (SF-36 baseline 55.67 ± 8.43; at 3 months 84.56 ± 11.56 *p*-value < 0.0001). In fact, during treatment, the number of sexual intercourses increased significantly thanks to the greater safety of women in dealing with sexual intercourse in absence of infections.

To avoid recurrence of the infection it is necessary to maintain a correct vaginal microenvironment with a correct regulation of the microbiota[23]. The function of HT seems to reduce the amount of candida without altering the quality and quantity of vaginal *lactobacilli*. Indeed, no other type of infection occurred during the treatment[24]. Moreover, the other components of the product (Tea Tree Oil, Tabebuia, Juglans Regia, Copper) are fundamental to complete the action of hydroxytyrosol, amplifying the effects and optimizing the natural functioning of the immune system. Actually they are natural molecules that increase the anti-inflammatory response while keeping stable the number of vaginal lactobacilli[25-29].

It is also interesting to note that menopausal patients treated in this study, already undergoing local estrogen therapy, having fewer candida episodes, have significantly improved their quality of life and sexual function. This could be related

to the synergistic action of the estrogen which improves the vulvovaginal atrophy and therefore the vaginal microbiota and the antifungal activity of HT.

Further, resistance mechanisms continue to change and evolve, challenging the medical clinic and exacerbating the need for discovering original therapies against *Candida* diseases. In this way, identification of new bioactive compounds as well as the development of original formulations of antifungals and combinations involving active biomolecules and agents represents the possibility for a successful therapeutic approach[30-33]. Another important data is the reduction of dysuria during treatment. It is well known that dysuria is frequently associated with RVVC and the affected often try to avoid sexual intercourse, as they think that pain is correlated to a possible post-coital infection[34-38].

Finally, women showed a high satisfaction level without adverse effects and almost every woman spontaneously decided to continue the treatment even after the conclusion of the study.

Conclusions

The strength of our study is the prospective design. The limitation is the not randomized study design without placebo group and the small number of patients. Further prospective studies are required to confirm efficacy and safety profiles of this product.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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