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Evaluation of the Effect of the Nifuratel - Nystatin Combination to Treat Bacterial Vaginosis in Postmenopausal Women, Armenia, Colombia, 2013-2016

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Abstract

Introduction: Bacterial vaginosis, or vaginal dysbiosis, is one of the most common vaginal conditions, characterized by a pathological change in the vaginal microbiota.

Objective: To establish the effect of the nifuratel - nystatin combination to treat bacterial vaginosis in postmenopausal women.

Materials and methods: Cohort study in 57 sexually active postmenopausal women, who consulted for vaginal discharge syndrome, in which the diagnosis of bacterial vaginosis was made; between 2013 and 2016. In a private clinic in Armenia (Colombia). The effect was evaluated by observing the disappearance of symptoms in the first follow-up (seven days after initiating the treatment) and with the Amsel criteria and the Nugent score one month after the end of therapy. The dose used was nifuratel 500 mg - nystatin 200,000 IU intravaginally daily for six days. Convenience sampling was conducted. Descriptive statistics were used.

Results: The mean age of the women was 57.36 ± 4.28 years. The most frequent symptom was white-grayish vaginal discharge in 91.22% of the participants, followed by bad odor in 85.96%. In the seven-day follow-up, the symptoms disappeared in 94.73% of the patients. In the month's follow-up, 89.47% of the women reported absence of symptoms; which was confirmed with the Amsel criteria and a median Nugent score of 3. Therapeutic failure, at one month, was 10.52% (n = 6/57). In none of the patients there were adverse reactions.

Conclusions: The nifuratel - nystatin combination reports a notable effect to treat bacterial vaginosis in postmenopausal women; being well tolerated and without adverse reactions. Randomized controlled clinical trials of its efficacy and safety in larger populations are required in order to establish recurrence rates.

Keywords: Vaginosis; Bacterial; Vaginitis; Postmenopause; Drug effects; Leukorrhea

Introduction

Vaginal discharge syndrome characterizes an inflammatory/ infectious process of the vulva and vagina, which is associated with three pathologies: Bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) and vaginal trichomonas's (VT); which is accompanied by various signs and symptoms (vaginal discharge, vaginal and/or vulvar erythema, vaginal and/or vulvar burning and / or itching, irritation, dysuria and dyspareunia, depending on the present condition); It occurs secondary to the invasion and multiplication of microorganisms, as a result of the environmental imbalance in the vaginal microbiota [1]. Bacterial vaginosis (BV), or vaginal dysbiosis, is characterized by a change in the vaginal microbiota dominated by Lactobacillus spp. (producers of lactic acid and hydrogen peroxide), generating an imbalance in the vaginal ecosystem, moving towards the colonization of anaerobic bacteria (Gardenella vaginalis, Mycoplasma hominis, Mobiluncus, Prevotella spp, Atopobium vaginae, among others) [1,2]. BV is a condition that affects between 30% and 60% of women worldwide [1,3]. It represents a public health problem among women of reproductive age, for their offspring and their partners; since it is associated with adverse reproductive health

outcomes such as: pelvic inflammatory disease (PID), spontaneous abortion, threatened preterm labor, premature delivery and increased risk of acquisition and transmission of the human immunodeficiency virus (HIV) [4-6]. It is known that between 50% and 80% of women can be asymptomatic for BV, with an adherent greyish-white discharge, bad odor, burning, irritation, vaginal itching and dysuria standing out in the symptoms [2,7]. The diagnosis of BV can be made clinically, through the Amsel criteria (Annex 1) and the Nugent score (Annex 2); considered as the "gold standard" throughout the world, for almost three decades, despite its limitations [8-11].

Annex 1. Amsel criteria	
1	pH of vaginal discharge > 4.5 [8]
2	Smell "fishy" when adding KOH10% to vaginal discharge
3	Presence of clue cells (guide)
4	Grayish-white discharge, homogeneous, thin and attached to the vaginal walls
The diagnosis of bacterial vaginosis is made with 3 of the 4 criteria.	

Annex 2. Nugent scoring system			
Punctuation	Lactobacillus spp (Gram positive rods)	Gardnerella vaginalis and Bacteroides spp. (Gram negative rods and cocci) [9]	Mobiluncus spp. (Curved Gram negative rods)
0	4+	0	0
1	3+	1+	
2	2+	2+	1+ o 2+
3	1+	3+	3+ o 4+
4	0	4+	
0) No morphotypes present; 1+) less than 1 morphotype present; 2+) 1-4 morphotypes present; 3+) 5 to 30 morphotypes present; 4+) 30 or more morphotypes present. The diagnosis of Bacterial Vaginosis is made when the score is ≥ 7.			

In the treatment of BV, oral metronidazole has been the drug of choice for several decades; however, all regimens have high recurrence rates (69% to 80%) in 12 months; which has led to the search for alternatives other than metronidazole [12-16]. Post menopause characterizes hypoestrogenism, resulting in the genitourinary syndrome of menopause [17]. Due to the decrease in estrogens, the glycogen content in the vaginal epithelium also decreases, leading to the depletion of lactobacilli spp. (Lactobacilli present during the reproductive period are reduced 10 to 100 times in the vaginal microbiota); This decrease leads to an increase in vaginal pH, because glucose is not converted to lactic acid [18,19]. The high pH promotes the growth of pathogenic bacteria, especially the colonization of Enterobacteriaceae [20]. At present, neither the diagnosis nor the treatment of BV in postmenopausal women are standardized; and knowing that postmenopausal women present twice more BV than women of childbearing age, it is necessary to opt for different alternatives to traditional treatments [21,22]. Nifuratel (a synthetic derivative of nitrofurans) shows strong antiprotozoal (trichomonacidal) and antibacterial activity, with a certain fungicidal effect, without being active against the physiological flora of lactobacilli spp; whose safety and therapeutic efficacy have been evaluated in more than 12,000 patients [23]. Extensive clinical experience confirms that nifuratel is effective and safe for the treatment of bacterial vaginosis, vulvovaginal candidiasis, and vaginal trichomoniasis, especially in women with mixed vaginitis [24]. As there are gaps in knowledge regarding the treatment of BV in postmenopausal women; and since there is not enough research in Colombia about other treatment options beyond metronidazole and clindamycin, a descriptive study was proposed whose objective was to establish the effect of the nifuratel-nystatin combination to treat bacterial vaginosis in postmenopausal women.

Materials and Methods

Design and population Cohort study

Sexually active women in natural post menopause, residents of Quindío (Colombia), who consulted for vaginal discharge syndrome were included; in which the diagnosis of bacterial vaginosis (BV) was made using the Amsel criteria and confirmed with the Nugent score (Annex 1 and 2), in a private clinic, of third level of complexity, reference center in the department from Quindío, and that serves the population belonging to the

contributory regime and the one subsidized by the State in the social security system in Colombia; between May 1, 2013 and April 30, 2016. Women who had received antibiotics during the last two weeks, those who used a vaginal douche or referred sexual intercourse during the 24 hours prior to the check-up, not having received hormone replacement therapy in the last six months, and data loss greater than 10% were excluded. A consecutive sampling was done and all women who met the inclusion and exclusion criteria were considered. Procedure Patients with a diagnosis of BV were selected, based on the identification of the following codes of the international classification of diseases (ICD10): N76.0-Acute vaginitis or N76.1-Subacute vaginitis, in which the Amsel criteria and Nugent score for BV were met. For women who met the selection criteria and agreed to participate in the study, the study objectives were explained to them, and after signing the informed consent, an Excel® 14.0 form was filled out, where the sociodemographic characteristics were recorded, clinical symptoms and clinical examination data. All the participants were evaluated by the main investigator; Speculoscopy was also performed, in order to evaluate flow characteristics (quantity, color, consistency and smell), and the presence of vulvovaginal signs (vulva, vaginal walls and cervix), among others. The nature of their clinical condition was explained to each patient, and intravaginal ovules of the combination nifuratel 500 mg - nystatin 200,000 IU were offered as a therapeutic option (every night at bedtime), for six (6) days, following the scheme, who state that the combination of nifuratel 500 mg + nystatin 200,000 IU once a day is the best dose (in terms of risk / benefit ratio) [25].

Collection and transport of samples

Vaginal pH was measured in each participant using a test strip (MQuant®), the amine test was performed with the application of 10% potassium hydroxide drops (10% KOH) to a sample of vaginal discharge; A sample of the vaginal discharge was taken with a cotton swab from the anterior cul-de-sac and lateral walls of the vagina, which was spread on a microscope slide with Gram stain in order to evaluate the presence of clue cells (guide) and the Nugent score.

Intervention [9]

The ovule with the combination of nifuratel 500 mg + nystatin 200,000 IU was applied at night, at bedtime, for 6 days. The treatment was delivered to each participant by a professional nurse in charge for this purpose, without the intervention of the researcher. A group of three nursing assistants were in charge of daily monitoring of each patient to ensure that the drug was applied in the indicated way, while at the same time investigating the presence of adverse reactions. Two (2) follow-ups were conducted: one week (seven days after the therapy started), and one month (thirty days after the therapy ended). In the first control, the absence or presence of symptoms was evaluated, and the appearance of adverse reactions was also investigated to assess safety. In the month's follow-up, the absence or presence of symptoms was taken into consideration to evaluate the therapeutic effect, as well as the Amsel criteria and the Nugent score in order to establish the presence of recurrences. The findings of each of the women were recorded in each control. The follow-up program was complemented with a communication telephone line, through which the group of nursing assistants monitored the application of the therapy on a daily basis and inquired about the presence of any adverse reaction. The procedures for data collection, completion and storage of information were standardized by training the nursing staff who supported the study by the main investigator. Adverse reactions were evaluated through the application of a survey, to each patient, in each of the controls; survey prepared by the research team; where the class, frequency and severity of each adverse reaction and the etiological role of the treatment were questioned.

Variables measured

Sociodemographic (age, ethnicity, level of education, marital status, socio-economic stratum, occupation, affiliation to the general health social security system, religion, area of residence), weight, height, BMI; time spent with a partner, age of menopause, evolution of time of menopause; habits (alcohol intake, smoking, sedentary lifestyle), medical history, sexual behavior variables (masturbation, oral sex, intercourse –vaginal or anal–, use of erotic toys, frequency of monthly sexual relations); history of bacterial vaginosis in the last year, incomplete treatment in episodes of previous bacterial vaginosis; presence or absence of the symptoms of bacterial vaginosis and adverse reactions. The Amsel criteria and the Nugent score were also evaluated.

Statistical analysis

Absolute and relative frequencies were calculated for the qualitative variables; in the quantitative variables, measures of central tendency (mean, median) and dispersion (standard deviation, percentiles, minimum value, maximum value and range) were used. The statistical analysis was done with the Epi Info® 7.2 programs. And Stata® 15.1.

Ethical aspects

The study was approved by the Ethics Committee of the participating institution. The requirements for medical research on human beings established in the Declaration of Helsinki and with Resolution 8430 of 1993 were met, which establishes the scientific, technical and administrative standards for health research. All participants signed the informed consent to enter the study. The confidentiality of the information was guaranteed.

Results

During the follow-up period, 3,157 women with bacterial vaginosis were treated at the institution, of which 429 (13.58%) met the inclusion criteria; 147 (34.26%) were excluded for having received antibiotics in the last two weeks, 135 (31.46%) for having used a vaginal douche, 49 (11.42%) because they reported sexual intercourse during the previous 24 hours and 41 (9.55%) for data loss greater than 10%. In the end, a sample of 57 patients was obtained. The mean age of the participants was 57.36 ± 4.28 years. 87.71% were of urban origin, 89.47% belonged to the contributory insurance scheme and 92.98% were Catholic. Table 1 describes the sociodemographic characteristics of the population (Table 1).

Table 1: *Sociodemographic characteristics of women with bacterial vaginosis, in Quindío, 2013-2016.*

Variable and categories	n(%)
Age: X ± SD years	57,36 ± 4,28
Age of partner: X ± SD years	59,61 ± 4,38
Weight: X ± SD Kg	67,95 ± 8,24
Height: X ± SD Cms	157,39 ± 4,82
BMI: X ± SD	27,63 ± 5,41
Race	
White	37 (64.91%)
Indigenous	7 (12.28%)
Afro Colombian %	13 (22.8 %)
Civil Status	
Married %	24 (42.1%)
Common Law	14 (24.56%)
Single	10 (17.54%)
Widows	9 (15.78%)
Occupation	
Housewives	34 (59.64%)
Employed	17 (29.82%)
Retired	6 (10.52%)
Socioeconomic status	
High	15 (26.31%)
Middle	36 (63.15%)
Low	6 (10.52%)
Educational level	
Primary	3 (5.26%)
Secondary	18 (31.57%)
Technical	21 (36.84%)
Professionals	15 (26.31%)

The mean age of menopause was 48.93 ± 5.71 years, with a mean duration of menopause of 8.95 ± 4.73 years. The time of living together as a couple was 16.27 ± 5.92 years. Alcohol intake was present in 68.42% of the women. 19.29% smoked, with a median consumption of 3 cigarettes per day (range between 3 and 9). Sedentary lifestyle was observed in 77.19%. In the medical history, it was observed that 40.35% had hypertension, 36.84% had dyslipidemia, 15.78% hypothyroidism, and 8.25% had type 2 diabetes. 8.77% had a history of breast cancer, and 12.28% had morbid obesity. A history of bacterial vaginosis in the last year was detected in 21.05% (n = 12/57) of the women; of which eight stated that they had not completed the treatment. In relation to the variables of sexual behaviour, masturbation was an experience barely explored by 14.03% of the women. Oral sex was the preferred sexual practice for 84.21%. Vaginal intercourse was practiced by 100%, while anal was reported by 12.28%. The frequency of monthly sexual intercourse yielded a median of 2 (range between 0 and 5). The use of erotic toys was detected in 22.8% of the participants. Upon entry to the study, 100% of the women were symptomatic. The symptoms reported by the patients, in order of frequency, are detailed in Table 2; being the grayish-white adherent discharge (91.22%) the most frequent, followed by bad odor (85.96%) and vaginal burning (75.43%). 75.43% (n = 43/57) presented four or fewer symptoms, 19.29% (n = 11/57) five, and 5.26% (n = 3/57) six or more symptoms; with a median of 4 (range between 3 and> 6) (Table 2).

Table 2: *Symptoms of postmenopausal women with bacterial vaginosis, in Quindío, 2013–2016.*

Symptoms	n (%)
Bad vaginal odor	49 (85.96%)
Clue cells (guide)	34 (59.64%)
Dysuria	5 (8.77%)
Grayish-white adherent discharge	52 (91.22%)
pH >4,5	41 (71.92%)
Vaginal burning	43 (75.43%)
Vaginal irritation	6 (10.52%)
Vaginal itching	14 (24.56%)

At one week of follow-up, the positive effect of the combination of nifuratel 500 mg + nystatin 200,000 IU was evident when the absence of symptoms was observed in 94.73% (n = 54/57) of the participants; presenting a total of 3 therapeutic failures (n = 3/57 = 5.26%), of which two were diabetic and one had morbid obesity. At one month of follow-up, 89.47% (n = 51/57) of the patients reported absence of symptoms, which was demonstrated with the Amsel criteria and confirmed with a median Nugent score of 3; In 5.26% there was a recurrence of the infection, which added to 5.26% of therapeutic failure, finally reported

10.52% (n = 6/57) of therapeutic failure; of which three were diabetic, two were morbidly obese and one was a sex worker. The initial median in the Nugent score was 8 (range between 7 and 10), decreasing to 3 (range between 0 and 7) at one month of follow-up. In none of the patients there were adverse reactions, therefore, there was no need to discontinue the medication; there was also no loss to follow up.

Discussion

In this study, it was observed that the therapeutic response of the nifuratel-nystatin combination, to treat bacterial vaginosis in postmenopausal women, at one week of follow-up, was present in 94.73% of the participants, managing to be maintained in 89, 47% at one month of follow-up; results that align with those, who in a group of 52 women (not pregnant), aged between 20 and 54 years, observed a good clinical and microbiological influence where the controls reported 89.5% and 84.2% respectively. For its part, another study concludes that treatment with the combination nifuratel - nystatin, in women with complaints of vaginal discharge and / or itching, is successful in all cases [26]. In the Czech Republic, in a participating population of 50 women with vaginal complaints, published that the therapy with the combination nifuratel 500 mg - nystatin 200,000 IU intravaginal, over a period of 7 days, exerts a high effect and a low number of relapses. A Bulgarian article from 1999, a study that included 159 women with vaginal infections (not pregnant) [28], aged between 15 and 54 years; indicates that the results obtained give reason to approve that the nifuratel - nystatin combination has a good chance of influencing mixed forms of vaginal infection, since an effect was found in 88.1% of the participants [29]. In the study in which they evaluated the in vitro activity of nifuratel on vaginal bacteria, suggesting that it has a better spectrum of activity against metronidazole and clindamycin, being highly active against Gardnerella vaginalis and Atopobium vaginae, without affecting lactobacilli; they also conclude that nifuratel is a potential candidate for the first-line treatment of BV. Another article, published in Italy in 2012, suggests that nifuratel is probably the most valid therapeutic agent for the treatment of BV [30]. In a meta-analysis, which included seven controlled clinical trials comparing nifuratel and metronidazole, performed in patients with vulvovaginal infections; in which a total of 1,767 patients participated, 832 of whom were treated with nifuratel and 935 with metronidazole. The results confirmed the equivalence between nifuratel and metronidazole, the overall proportion of patients cured in the two groups was 88.5% and 90.0%, respectively, in the presence of homogeneity between the studies (p = 0.342); however, some research has shown that the cure rate of nifuratel in patients with mixed Trichomonas vaginalis + Candida or Trichomonas vaginalis + infections or with bacterial vaginosis and mixed bacterial flora, is higher than that of metronidazole, due to the broad spectrum of action of nifuratel [23]. A systematic review of the literature reports that nifuratel has a strong trichomonacidal activity equivalent to that of metronidazole; it has a broad spectrum of antibacterial action, which includes both Gram positive and Gram negative bacteria; it is active against Chlamydia trachomatis and Mycoplasma spp. and it also has some degree of activity against Candida spp. Its broad spectrum of action, confirmed by in vitro and in vivo studies, covers practically all microorganisms responsible for genitourinary tract infections [31]. Its toxicological profile makes it very safe, being practically non-toxic, and well tolerated after repeated intravaginal administrations. The comparison between past and recent clinical studies confirms that, unlike metronidazole, no phenomena of resistance to treatment with nifuratel are reported. It can be used in adolescents, in lactation and during pregnancy, due to the absence of teratogenic effects. In conclusion, nifuratel shows a very favorable risk / benefit ratio for the treatment of patients with vulvovaginal infections. Based on the above and in conjunction with our results, we can assure that the nifuratel 500 mg - 200,000 IU intravaginal nystatin combination continues to be effective against bacterial vaginosis (BV) with low recurrence rates and no adverse reactions; For this reason, we consider that this medicine could be the replacement of traditional therapies [32,33]. The main strength of this research consists of being the first study carried out in Colombia, in a postmenopausal population, with the use of the combination nifuratel 500 mg - nystatin 200,000 IU intravaginal, as well as the use of endorsed and easily reproducible clinical criteria (criteria Amsel and Nugent score). Another strength is the complete follow-up of all participants after 30 days. Among the weaknesses is the small size of the sample, the fact that it was conducted in a single institution, in addition to the weaknesses of a prospective cohort study such as its cost.

Conclusions

The nifuratel-nystatin combination has a significant effect in treating bacterial vaginosis in postmenopausal women, being well tolerated and without adverse reactions; retaining itself as an adequate treatment option, despite its age. Randomized controlled clinical trials on the efficacy and safety of this combination are required in larger populations in order to establish the eventuality of recurrence rates. Such investigations must face the reality that conventional therapies offer unsatisfactory results, due to high recurrence rates.

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