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Efficacy and safety of the combination nifuratel-nystatin and clindamycin-clotrimazole, in the treatment of bacterial vaginosis. Randomized controlled clinical trial

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Abstract

Introduction: Bacterial vaginosis (BV) is the most frequent gynecological infection in women of reproductive age, thus driving the search for effective and safe treatments.

Objective: To compare the efficacy and safety of the combination nifuratel-nystatin and clindamycin-clotrimazole, in the treatment of bacterial vaginosis.

Materials and Methods: Randomized controlled clinical trial in 147 single women (18 to 39 years old), non-pregnant and sexually active, with a diagnosis of BV according to the Amsel clinical criteria and the Nugent score; between 2016 and 2018. In a highly complex private clinic in Armenia, Colombia. Women were randomized into two groups: "A" (73 participants: nifuratel (500 mg) - nystatin (100,000 IU) and "B" (74 participants: clindamycin (100 mg) - clotrimazole (200 mg)); both groups were treated with vaginal ovules, "A" for six days and "B" for three days. All participants were followed-up for clinical and microbiological healing at 7 and 30 days, respectively, after completion of treatment, the STATA® 14.0 program was used.

Results: The mean age of women was 28.35±5.79 years. The clinical cure rate with the nifuratel-nystatin combination was 93.15%, and that of clindamycin-clotrimazole 97.29%, (p=0.123). The microbiological cure rate with the nifuratel-nystatin combination was 87.67%, and that of clindamycin-clotrimazole 93.24%, (p=0.102). Regarding safety, there were also no significant differences between the two groups (p=0.144); Mild adverse reactions were observed. Recurrence in group "A" was 12.32% compared to 6.75% in group "B" (p>0.05).

Conclusions: In this study, the combinations nifuratel (500 mg) -nystatin (100,000 IU) and clindamycin (100 mg)-clotrimazole (200 mg), reported that both are equally effective and safe options in the treatment of BV. It is necessary to evaluate the effect and safety of other combinations in order to implement timely interventions.

Keywords: Vaginosis; Bacterial; Efficacy; Safety; Nifuratel; Nystatin; Clindamycin; Clotrimazole.

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Introduction

Bacterial vaginosis (BV) is a common vaginal infection, which affects 1/3 of the population of women of childbearing age; representing the most common vaginal infection in women between 15 and 44 years old [1,2]. BV is a dysbiosis that is part of the "vaginal discharge syndrome"; represents a change in the balance of the vaginal microflora, characterized by an increase in vaginal pH, a reduction in lactobacilli spp. (producers of hydrogen peroxide and lactic acid), and an increase in facultative and anaerobic bacteria (*Ureaplasma, Mycoplasma, Gardnerella vaginalis, Prevotella, Peptostreptococcus and Bacteroides spp*.) [2,3]. The prevalence of BV differs widely from country to country, within the same region, and even within similar population groups; it is estimated to range from 8% to 75% [4,5]. The risk factors for BV include: race, non-use of a condom, two or more male sexual partners, age 30 to 49 years, low educational level, use of hormonal contraceptives, smoking, douching, intrauterine device (IUD), among others [6-8]; and although BV is not considered a sexually transmitted infection (STI), it does show a similar epidemiological profile [7,9]. Signs and symptoms of BV may include increased vaginal discharge, which is homogeneous, grayish-white in color, with a "fishy odor" (more noticeable after intercourse or menstruation), dyspareunia, dysuria, sinusorrhagia, etc.; however, more than 50% of women are asymptomatic [2,10].

The diagnosis of BV can be made clinically using the Amsel criteria [11] and with the help of the laboratory using the Nugent scoring system [12]; that has been considered the "gold standard" for the last thirty years; however, salt microscopy, wet mount microscopy, chromogenic tests (OSOM® BVBlue®: detect elevated levels of the enzyme sialidase), and ion motility spectrometry (IMS) (VGTest ™ IMS: determine levels of malodorous biogenic amines associated with BV) [13,14]; or by molecular techniques (BD Affirm ™ VPIII probe assay) [15] and nucleic acid amplification tests (NAATs) [16]. Metronidazole, tinidazole, and clindamycin have been approved for the treatment of BV; with similar efficacy when administered locally in the vagina or orally; with cure rates of approximately 58% to 92%, after 1 month. The recommended doses are 500 mg of oral metronidazole twice a day for 5 days, clindamycin 2% vaginal cream once a day for 7 days, oral clindamycin 300 mg twice a day for 7 days, metronidazole vaginal gel at 0,75% once daily for 5 days or oral regimens of 2 grams of metronidazole or tinidazole in a single dose [2,17,18].

Nifuratel, a derivative of furans, has a broad spectrum of antibacterial and trichomonacidal action equivalent to that of metronidazole or clindamycin; that includes both gram-negative and gram-positive organisms, with a safe toxicological profile and no teratogenic effects; therefore, it can be used during pregnancy [19]. This has demonstrated, for several years, its efficacy and safety in the treatment of different vulvovaginal infections [20-22]. In relation to the multiple therapeutic options for BV, the

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objective of this study arises to compare the efficacy and safety of the combination nifuratel-nystatin and clindamycin-clotrimazole, in the treatment of bacterial vaginosis, through the evaluation of the rate of clinical and microbiological healing.

Materials and Methods

Design and population

A triple blind randomized controlled clinical trial was conducted. Single women between 18 and 39 years old, non-pregnant, sexually active and who went to the office for "vaginal discharge syndrome" (infectious condition of the vagina, characterized by one or more of the following symptoms: discharge, burning, irritation, vulvar itching, dysuria, dyspareunia and / or vaginal stench) [2], which were diagnosed with BV according to the Amsel clinical criteria [11] and confirmed with the Nugent score [12]. Between July 1, 2016 and June 30, 2018. In a highly complex private clinic in Armenia, Colombia; reference center in the department of Quindío, which provides services to the population belonging to the contributory regime and subsidized plans of the Colombian health care insurance system. The sample size was calculated in comparable populations. The number of participants needed to detect a standardized difference in response to treatment between the groups was calculated at 120 (60 per group) with a statistical power of 80% using a cut-off score for statistical significance of 20% and considering up to a 15% loss to follow-up, in this way 73 participants were included in group "A" and 74 in group "B". Simple random sampling was performed using a table of random numbers with a hidden randomization sequence, considering all women who met the inclusion criteria. Women with diabetes mellitus, any type of cancer, undergoing treatment with glucocorticoids or immunosuppressants, antibiotic treatment or vaginal ovules in the previous two weeks, sexual intercourse within 72 hours prior to the check-up, hypersensitivity to drugs, not completing the full treatment and diagnosis of trichomoniasis were excluded.

Procedure

Women from the gynecological consultation who attended for "vaginal discharge syndrome" and who were diagnosed with BV were selected, using the Amsel criteria [11] and the Nugent score [12]. The patients who met the selection criteria and agreed to participate in the study, the objectives of the research 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 physical examination data. Data collection was performed by a professional nurse hired for this research. Women were evaluated by the principal investigator; speculoscopy was performed in order to evaluate the characteristics of the discharge (quantity, color, consistency and smell), and the presence of vulvovaginal signs (vulva, vaginal walls and cervix), among others.

Collection and transport of samples

A sterile cotton swab was used to collect discharge samples from the lateral vaginal walls and the posterior cul-de-sac; which was immediately placed on three microscope slides. 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. Microscopic observation with Gram stain was made in order to evaluate the presence of guide (Clue) cells and the Nugent score. The diagnosis of BV was made with the presence of three of the four Amsel clinical criteria and a Nugent score ≥7. The reading of the samples was conducted by a bacteriologist specialized in microbiology, who is part of the staff of the participating clinic; following the protocols established by the

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Institution's Microbiology Laboratory. A nurse practitioner, outside the study, was in charge of randomization and assignment to groups "A" or "B". Triple blinding was ensured by ensuring that neither the participants, nor the researchers, nor the data collectors, nor those who analyzed them knew the type of drug combination that would be administered to each woman. Allocation concealment was done with opaque envelopes ordered and numbered by the pharmacy manager, who was not involved in the study.

Intervention

The group: "A", was made up of 73 women, those who received ovules with the combination nifuratel (500 mg) - nystatin (100,000 IU) for six days (at bedtime); Group "B" was made up of 74 women, who received the combination of clindamycin (100 mg) - clotrimazole (200 mg) for three days (at bedtime); according to CDC (Centers for Disease Control and Prevention) treatment guidelines (23). Each participating woman was followed-up control, at 7 days and 30 days, after having finished the complete treatment. In the 7-day follow-up, the absence or presence of symptoms was taken into account, as well as the Amsel criteria to establish the clinical cure rate; In the 30-day follow-up, the Nugent score was also evaluated, in order to establish the microbiological cure rate, for which a score ≤3 was validated, as well as the presence of failures or recurrences; They were also questioned about the possibility of adverse reactions. In the control and follow-up, a specialist in gynecology, external to the investigation, was assigned. The study program was complemented with a communication telephone line, through which a nursing assistant monitored daily the application of the ovules and investigated the presence of any adverse reaction. The presence of adverse reactions that were reported by the participating women were recorded on an adverse event report sheet, by a professional nurse, who did not belong to the research group.

Measured variables

Sociodemographic (age, ethnicity, area of residence, level of education, socio-economic stratum, occupation, affiliation to the general health social security system, religion), weight, height, BMI; presence or absence of the symptoms of bacterial vaginosis and adverse reactions. The Amsel criteria and the Nugent score were also evaluated before and after the follow-up (at 7 and 30 days after the end of the treatment).

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. Statistical analysis was done with the STATA® 14.0 program. Student's "t" tests were used to determine the difference between the means of the two groups; Fisher's test and Mann-Whitney U test to evaluate the association between two qualitative and quantitative variables.

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 were met. All participants signed the informed consent to enter the study. The confidentiality of the information was guaranteed.

Results

In the follow-up period, 2874 women with bacterial vaginosis (BV) were diagnosed in the participating clinic, equivalent to 36.39% of the

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population of non-pregnant women who consulted the gynecology service. Of the 2,874 women with BV, 1,431 (49.79%) did not meet the inclusion criteria; Of the remaining 1,443, 125 (8.66%) were excluded due to diabetes mellitus, 89 (6.16%) due to cancer, 72 (4.98%) due to being in treatment with glucocorticoids or immunosuppressants, 173 (11.98%) for being in treatment or having received antibiotics or vaginal ovules in the previous two weeks and 435 (30.14%) because they had sexual intercourse during the 72 hours prior to the check-up. At the end, the randomization was done with a population of 549 patients, of which a total of 147 women were selected for the investigation, 73 in group "A", and 74 in group "B", who completed the study. The mean age of the participants was 28.35±5.79 years. 87.75% were of urban origin, 89.79% belonged to the contributory insurance scheme and 94.55% were Catholic. 12.24% had obesity. No statistically significant differences were observed between the two groups in terms of sociodemographic characteristics (p>0.05) (Table 1).

Table 1: Sociodemographic characteristics of women with bacterial vaginosis, in Quindío, 2016-2018

Variable and categories	Group «A» (n=73)	Group «B» (n=74)	p
Age: X±SD years	28,59±6,13	28,13±5,42	NS
Age of couple: X±SD years	31,47±7,25	32,65±8,19	NS
Weight: X±SD Kg	62,41±5,78	63,71±4,89	NS
Height: X±SD Cms	162,05±3,94	160,98±4,05	NS
BMI: X±SD	24,19±3,57	24,75±4,19	NS
Race			
White	35 (47,94%)	38 (51,35%)	NS
Afro Colombians	27 (36,98%)	24 (32,43%)	NS
Indigenous	11 (15,06%)	12 (16,21%)	NS
Occupation			
Stay-at-home spouses	31 (42,46%)	30 (40,54%)	NS
Employees	33 (45,2%)	31 (41,89%)	NS
Unemployed	9 (12,32%)	13 (17,56%)	NS
Socio-economic levels			
High	21 (28,76%)	24 (32,43%)	NS
Middle	39 (53,42%)	42 (56,75%)	NS
Low	13 (17,8%)	8 (10,81%)	NS
Educational level			
Primary	3 (4,1%)	3 (4,05%)	NS
Secondary	18 (24,65%)	15 (20,27%)	NS
Technical	33 (45,2%)	36 (48,64%)	NS
Professional	19 (26,02%)	20 (27,02%)	NS

100% of the participants presented symptoms associated with BV. The signs and symptoms reported by the women are detailed in Table 2; being the adherent discharge of white-grayish color the most frequent in both groups (93.15% versus 95.94%), (p> 0.05); followed by bad smell (84.93% versus 86.48%), (p> 0.05); and pH> 4.5 (75.34% versus 72.97%), (p> 0.05). In the general population, 78.23% (n=115/147) of the women had four or fewer symptoms and 21.76% (n=32/147) had five or more symptoms, with a median of 4 (range between 3 and 8).

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Table 2: Symptoms of women with bacterial vaginosis, in Quindío, 2016-2018.			
Symptoms	**Grupo «A» n=73 (%)**	**Grupo «B» n=74 (%)**	**p**
Vaginal burning	53 (72,6%)	55 (74,32%)	NS
Clue cells (guide)	43 (58,9%)	45 (60,81%)	NS
Dysuria	7 (9,58%)	6 (8,1%)	NS
Vaginal irritation	8 (10,95%)	9 (12,16%)	NS
Bad vaginal odor	62 (84,93%)	64 (86,48%)	NS
pH>4,5	55 (75,34%)	54 (72,97%)	NS
Vaginal itching	18 (24,65%)	20 (27,02%)	NS
Grayish-white adherent discharge	68 (93,15%)	71 (95,94%)	NS

At the 7-day follow-up, the clinical cure rate (demonstrated with the Amsel criteria), with the nifuratel-nystatin combination, was 93.15%, observing the absence of symptoms in 68 of the 73 participants; while the clinical cure rate of the clindamycin-clotrimazole combination was 97.29%, as the absence of symptoms was observed in 72 of the 74 participants (p=0.123). At 30 days after completing the complete treatment, the microbiological cure rate (confirmed with a median Nugent score ≤3), with the nifuratel-nystatin combination, was 87.67% (n=64/73), and that of clindamycin-clotrimazole of 93.24% (n=69/74), (p=0.102). At 30 days, the Nugent score, in group "A", reported 9 therapeutic failures (12.32%), of which three were diabetic, two had a history of recurrent BV, two had morbid obesity and two were smokers of more than 20 cigarettes a day. In group "B", 5 therapeutic failures were reported (6.75%), two were diabetic, two had a history of recurrent BV, and one was a smoker of more than 20 cigarettes a day; without finding a statistically significant difference (p>0.05). It was observed that in group "A" there was a 12.32% recurrence compared to 6.75% in group "B", with no statistically significant difference ((p> 0.05). Regarding safety, there were also no significant differences between the two groups (p=0.144); Mild adverse reactions were observed (Table 3), none serious, and there was no need to suspend therapy; neither did any loss of patients occur to follow-up.

Table 3: Adverse reactions of the combination nifuratel-nystatin and clindamycin-clotrimazole, in women from Quindío, 2016-2018.			
Adverse reactions	Grupo «A» (n=73)	Grupo «B» (n=74)	p
Burning	2 (2,73%)	4 (5,4%)	NS
Local irritation	1 (1,36%)	2 (2,7%)	NS
Itching / Pruritus	1 (1,36%)	4 (5,4%)	NS
Vaginal bleeding	1 (1,36%)	2 (2,7%)	NS
Dysuria	2 (2,73%)	4 (5,4%)	NS
Burning sensation	3 (4,1%)	5 (6,75%)	NS

Discussion

In this investigation, it was found that at seven days of follow-up, the clinical cure rate with the nifuratel-nystatin combination was 93.15%, compared to 97.29% with the clindamycin-clotrimazole combination, (p=0.123); while at thirty days, the microbiological cure rate was 87.67% and 93.24%, respectively, (p=0.102); There were also no significant differences in the presence of adverse reactions between the groups (p=0.144), which were mild, and none were serious. The results of this study are similar to those reported by Zlatkov et al. [24], in Bulgaria, who established the clinical and microbiological cure of the patients treated with nifuratel-nystatin (the efficacy reached 89.5% and 84.2%, respectively); being consistent with 88.1% and 86.8% described by Karag'ozov et al. [25]. Which aligns with the conclusions of

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Ahmed-Jushuf et al. [26], in Nottingham (England), who state that a 3-day course of clindamycin is an effective and well-tolerated treatment for BV. This is similar to the 93.5% cure of BV, 7 days after therapy, with persistence of cure in 89.7% (one month after treatment), reported by Livengood et al. [27], in Durham, North Carolina (USA). Regarding safety, regarding the appearance of adverse reactions, the results of this research are within those reported by other authors [28-30]; those who conclude that a 3 to 7-day cycle of vaginal clindamycin is well tolerated. In relation to nifuratel-nystatin, the safety is comparable to that published by the group of experts representing the Polish Gynecological Society [31], being consistent with the findings of Polatti et al. [32], although this study involved a population of women with trichomoniasis and / or candidiasis.

In the presence that the clinical approaches currently available for the treatment of BV are somewhat empirical, in addition to involving the use of nitroimidazoles or clindamycin (antimicrobials with broad spectrum anaerobic coverage) [2,23], whose recurrence rates they are up to 50% within the following 6 to 12 months after treatment [33]; These forces the search for other alternative therapeutic approaches, that are not only more effective but safer, and hopefully with shorter treatment cycles, in order to guarantee compliance. The main strength of this study is found in the use of "gold standard" diagnostic methods for more than three decades, as well as the selection processes of the participants, in addition to being the first study to demonstrate that the nifuratel- nystatin and clindamycin-clotrimazole are equally effective in treating BV. The limitations include the number of patients included in each group; however, it was possible to obtain an adequate number of women, with homogeneous characteristics, to evaluate the efficacy and safety of the two types of combinations.

Conclusions

In this investigation, the combinations nifuratel (500 mg)-nystatin (100,000 IU) and clindamycin (100 mg) -clotrimazole (200 mg), were reported as equally effective and safe options in the treatment of BV, although they were observed mild adverse reactions, but none serious. Studies with a control group and random assignment are required in order to evaluate the effect and safety of other combinations, in order to provide better evidence regarding this management, to help implement timely interventions, to minimize recurrences.

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