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Original Article

Assessment of efficacy of ketoconazole/clindamycin vs metronidazole/nystatin in candidiasic vaginitis and bacterial vaginosis.

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ABSTRACT

Background: The term vaginitis refers to vaginal mucosa's inflammation, which produces a great variety of symptoms, including: abundant genital draining, of different color, fetid odor, pruritus, irritation, heat, dyspareunia, underwear spotting and frequently it is related to burning when urinating.
Objective: To compare the ketoconazole/klindamycin *vs* metronidazole/nystatin efficacy for the treatment of vaginitis.
Material and Methods: Efficacy of the ketoconazole/klindamycin vs metronidazole/nystatin combination to vaginally treat *Candida* albicans vaginitis, bacterial vaginosis and mixed vaginosis was compared. Seventy patients with diagnosis of candidiasic vaginitis and bacterial vaginosis were included in a longitudinal, prospective, double-blind study. Patients were treated with ketoconazole/clindamycin vaginal tablets and metronidazole/nystatin in ovules. Patients were evaluated at baseline and at day 7.
Results: The global result showed that ketoconazole/clindamycin is superior to metronidazole/nystatin in the treatment of vaginitis/vaginosis. *C. albicans* was isolated in 23 patients, 12 in the ketoconazole/clindamycin group and 11 in the metronidazole/nystatin group. At the end of the study, cultures were negative in 66.7% of ketoconazole/clindamycin group and in 54.5% of metronidazole/nystatin group. Eighteen cases presented mixed vaginitis, 13 in ketoconazole/clindamycin group and 5 in metronidazole/nystatin. At the end of the study, culture was negative in ketoconazole/clindamycin (83.3%) group and in all metronidazole/nystatin cases. Anaerobes were isolated in 21 patients, 9 in ketoconazole/clindamycin group and 12 in metronidazole/nystatin. At the end of the treatment, cultures were negative in 77% of ketoconazole/clindamycin group and in 66% of metronidazole/nystatin group; adverse reactions were not reported.
Conclusions: Treatment with ketoconazole/clindamycin for vaginitis/vaginosis is similar to that of metronidazole/nystatin. Microbiologically and clinically, treatment was well tolerated since there were no adverse reactions during its course.
Keywords: Vaginitis, vaginosis, ketoconazole, clindamycin.

RESUMEN

Antecedentes: el término vaginitis se refiere a la inflamación de la mucosa vaginal, la cual produce gran variedad de síntomas, que incluyen: escurrimiento genital abundante, de diferente coloración, de olor fétido, prurito, irritación, ardor, dispareunia, manchado de la ropa interior y frecuentemente se relaciona con ardor al orinar.
Objetivo: comparar la eficacia de ketoconazol/clindamicina contra nistatina/metronidazol, ambas por vía vaginal, para el tratamiento de la vaginitis.
Material y métodos: se comparó la eficacia de la combinación de ketoconazol/clindamicina contra metronidazol/nistatina por vía vaginal en el tratamiento de la vaginitis por *Candida albicans*, vaginosis bacteriana y vaginosis mixtas. En un estudio longitudinal, prospectivo y doble ciego se incluyeron 70 pacientes con diagnóstico de vaginitis candidiásica y vaginosis bacteriana. La duración del tratamiento fue de seis días y se utilizó ketoconazol/clindamicina en tabletas vaginales y metronidazol/nistatina en óvulos. Se les revisó al ingreso (basal) y al séptimo día.
Resultados: el resultado global muestra que ketoconazol/clindamicina es superior a metronidazol/nistatina en el tratamiento de la vaginitis y vaginosis. Se cultivó C. albicans en 23 pacientes, 12 en el grupo de ketoconazol/clindamicina y 11 en el grupo de metronidazol/ nistatina. Al finalizar el estudio, el cultivo fue negativo en 66.7% del grupo ketoconazol/clindamicina y en 54.5% del grupo metronidazol/ nistatina. Dieciocho casos tuvieron vaginitis mixta, 13 en el grupo ketoconazol/clindamicina y 5 en el metronidazol/nistatina. Al final del estudio, el cultivo fue negativo en 83.3% del grupo ketoconazol/clindamicina y en todos los casos del grupo metronidazol/nistatina. Se aislaron anaerobios en 21 pacientes, 9 en el grupo ketoconazol/clindamicina y 12 en el otro. Al final del tratamiento, el cultivo fue negativo en 77% del grupo ketoconazol/clindamicina y en 66% del grupo metronidazol/nistatina. No se reportaron reacciones adversas en ninguno de los grupos. **Conclusiones**: el tratamiento con ketoconazol/clindamicina para la vaginitis y vaginosis es similar al de la combinación metronidazol/ nistatina. Desde el punto de vista microbiológico y clínico, el tratamiento fue bien tolerado, puesto que no se encontraron reacciones adversas durante su curso.
Palabras clave: vaginitis, vaginosis, ketoconazol, clindamicina.

SOMMAIRE

Antécédents : le terme vaginite fait référence à l'inflammation de la muqueuse vaginale, laquelle produit une grande variété de symptômes, qui comprennent : écoulement génital abondant, de coloration différente, d'odeur fétide, prurit, irritation, ardeur, dyspareunie, souillure des linges de corps et on la relie fréquemment avec ardeur au moment d'uriner.
Objectif : comparer la relation de kétoconazole/clindamycine contre l'administration de nystatine/métronidazole, toutes les deux par voie vaginale pour le traitement de ces maladies cliniques.
Matériel et méthodes : on a comparé l'efficacité de la combinaison de kétoconazole/clindamycine contre métronidazole/nystatine par voie vaginale dans le traitement de la vaginite par *Candida albicans*, vaginose bactérienne et vaginoses mixtes. Dans une étude longitudinale, prospective et en double aveugle on a inclut 70 femmes avec un diagnostic de vaginite candidosique ou vaginose bactérienne. La durée du traitement a été de six jours et on a utilisé kétoconazole/clindamycine en comprimés vaginaux ou métronidazole/ nystatine en ovules. On les a révisées au moment de l'entrée (basale) et au septième jour.
Résultats : on a cultivé *C. albicans* chez 23 patientes, 12 dans le groupe kétoconazole/clindamycine et 11 dans le groupe métronidazole/ nystatine ; au moment de terminer l'étude la culture a été négative en 66.7% du groupe kétoconazole/clindamycine et en 54.5% du groupe métronidazole/nystatine. En 18 cas il y a eu vaginite mixte, 13 dans le groupe kétoconazole/clindamycine et 5 dans le métronidazole/ nystatine ; à la fin de l'étude la culture a été négative en 83.3% des patientes avec kétoconazole/clindamycine et dans tous les cas du groupe métronidazole/nystatine. On a isolé des anaérobes chez 21 patientes, 9 dans le groupe kétoconazole/clindamycine et 12 dans le métronidazole/nystatine ; à la fin du traitement la culture a été négative en 77% des cas du groupe kétoconazole/clindamycine et en 66% du groupe métronidazole/nystatine. On n'a pas reporté des réactions adverses pour aucun groupe.
Conclusions : du point de vue microbiologique et clinique, le traitement pour la vaginite ou vaginose avec kétoconazole/clindamycine est pareil à la thérapeutique avec métronidazole/nystatine. Le traitement a été bien toléré, du fait qu'on n'a pas trouvé des réactions adverses pendant son cours. Le résultat global montre que kétoconazole/clindamycine est supérieur à métronidazole/nystatine pour le traitement de la vaginite ou vaginose.
Mots clés : vaginite, vaginose, kétoconazole, clindamycine.

Vaginitis refers to inflammation of the vaginal mucosa, which produces a wide variety of symptoms such as: Abundant genital runoff of different color (green, yellow, gray, white, etc.) and foul odor, itching, irritation, burning, dyspareunia, stained underwear, and often, burning with urination (dysuria). There are many potential causes of vaginal infection; those of bacterial, fungal or mixed origin account for most cases. Also, there are trichomonas vaginitis and viruses.

Bacterial vaginosis is the most common form and occurs in between 35 and 50% of the cases; *Candida* vaginitis is second with 20 and 40%, and less frequently trichomoniasis, which occurs in 10 to 30% of all cases. Also, mixed infections coexist. In a review of 1,000 consecutive patients, Gardner and Dukes found more than one pathogenic microorganism in 23.3% of patients with bacterial

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vaginosis and 17.7% with candidiasis.[1,2,3] Bacterial vaginosis is a vaginal infection that is now recognized as a risk factor with serious pelvic and obstetric complications. It includes premature membrane rupture, chorioamnionitis and fetal loss, postpartum endometritis and infection of the urinary tract.[2,3,4] It is related to sexual activity, especially with multiple partners, trichomoniasis, use of intrauterine devices and tampons.

However, it is also diagnosed in 29% of women who have not had sex.[1,2,3]

Gardnerella vaginalis is a facultative aerobic bacillus, present in 95% of patients with bacterial vaginosis and in 40 to 68% of asymptomatic women.[5]

Mobiluncus spp. was recently present in 50% of patients with bacterial vaginosis. These are anaerobic, small, mobile bacteria, with a large amount of flagella.[6] These bacteria are not part of the normal flora of the vagina.

Candida albicans is a commensal organism found in most patients that becomes an opportunistic pathogen when there is loss of ecosystem balance. Generally, fungal growth is limited by a competitive metabolism and production of fungal-specific inhibitors; *Lactobacillus* spp. *Candida albicans* is

found in 10 to 22% of asymptomatic women. It causes 20 to 40% of all vaginitis cases and 80 to 90% of fungal vaginitis. Several factors predispose to vaginal candidiasis such as pregnancy, systemic antibiotic therapy, diabetes mellitus, steroids, oral contraceptives, immunological disorders, sexual practices and others.[2,3] Often, vaginal candidiasis coexists with some other vaginal pathogens, causing mixed infections.[6]

Amsel's and collaborators criteria were used for vaginosis diagnostic:[5,7,8,9] to) homogeneous, non-inflammatory discharge, which adheres to vaginal walls; b) vaginal discharge with pH greater than 4.5; c) key cells, d) fishy (amine) smell in vaginal discharges before or after adding potassium hydroxide (smell test). Bacterial vaginosis may be diagnosed when three of the four criteria are present.[7,8,9]

Numerous treatment regimens were attempted, which included nitroimidazoles (metronidazole, tinidazole), clindamycin, ampicillin, tetracycline, and cephalosporins. Clindamycin is active against most Gram negative and Gram positive anaerobic and microaerophilic microorganisms.[9-12]

Candida vaginitis is treated topically with ketoconazole, miconazole, clotrimazole, or nystatin. Azoles are more effective than nystatin and relieve symptoms in 80 to 90% of patients. Single-dose treatments are restricted to mild, not complicated episodes, and it is preferable to use diagrams of three to seven days. Also, azoles administered orally for one to five days are effective for candidiasic vaginitis treatment; however, it should be noted the possibility of toxicity, in particular by the drug interaction.[13]

Administered vaginally, clindamycin phosphate proved to be useful in the treatment of bacterial vaginosis caused by *Gardnerella vaginalis*, *Mobiluncus* spp. and *Bacteroides spp.*[8,10,11,14 -17]

Because it is one of the main causes of gynecological consultation and with the intention of having an option in the treatment of bacterial vaginosis, Candida vaginitis and mixed vaginitis, a study is proposed where ketoconazole/clindamycin and nystatin/metronidazole are administered (both vaginally) for treatment of these conditions.

PATIENTS AND METHOD

Seventy patients between 18 and 60 years old who met the following inclusion criteria: diagnosis of vaginitis by Candida albicans and bacterial vaginosis, laboratory confirmation of infection by *C. albicans* (culture and microscopy), G. *vaginalis, Mobiluncus* spp. (culture) in the vaginal smear. No *Trichomonas vaginalis* or another protozoan, or *Neisseria gonorrheae*, *Chlamydia trachomatis* infections and viral infections (genital herpes, human papillomavirus) were found. Non-pregnant patients, without diabetes mellitus and who agreed to sign the form of acceptance and informed consent participated in a longitudinal, prospective, double-blind study to compare the efficacy of the combination of ketoconazole/clindamycin (KC) versus metronidazole/nystatin (MN). At the time of inclusion, patients underwent physical examination and vaginal discharge samples for culture in order to confirm some of the microorganisms under study. An appointment was made seven days later to determine the result of the culture and, if they met the inclusion criteria, patients were assigned to a treatment group. They were assigned randomly and divided into two treatment groups: one group (35) received ketoconazole at a rate of 400 mg + clindamycin 100 mg and a vaginal tablet every 24 hours for six days. The other (35) received metronidazole at a dose of 500 mg + nystatin 100,000 IU and an ovule every 24 hours for six days. Sealed envelopes with individual identification codes for each treatment were delivered to a person outside the research group. The study medication was stored in the hospital pharmacy. The attending physician wrote in the prescription the case number and the name of the study so that the pharmacist would provide the medication to the patient. Neither the patient nor the investigator or the nursing team knew what type of treatment patients were receiving, in order to keep the blind characteristic of the study.

During the course of treatment the use of any other drug vaginally such as antifungals (ketoconazole, itraconazole, fluconazole) or orally as antiparasitic agents (metronidazole, tinidazole, coated secnidazole) was prohibited. Sex abstinence was also requested.

Patients were observed on days 0 (baseline) and 7 (end of treatment). The physician performed an evaluation in each visit and it was required to fill out the symptoms and signs questionnaire. Samples were obtained from vaginal discharge for fungal and bacterial cultures. Clinical response was considered for treatment evaluation purposes. It indicated the disappearance of symptoms, genital itching and abnormal runoff on day seven of treatment; microbiological response noted the negativization of culture for microorganisms initially isolated in the culture carried out at the end of treatment (day seven). By the end of the study, patients were asked to assess the adverse effects of therapy.

Statistical Method

The effectiveness analysis included patients who completed all follow-up visits, while safety analysis included those who received one or more doses of the medication.

All statistical tests were two-tailed. The results in which the value of *p* was less than or equal to 0.05 had a significance level. The analysis of results was performed using SPSS software version 9.0; continuous variables were assessed using Student's t test and categorical variables with Pearson's chi-square test or Fisher's exact test. The results in both groups were compared.

RESULTS

Seventy patients were randomly assigned in two treatment groups; 35 were treated with ketoconazole/ clindamycin (KC) and 35 with metronidazole/ nystatin (MN). Eight (11.42%) patients discontinued the study when they did not return to the assessment on day seven (final). Of these dropouts, 1 (2.85%) was from KC group and 7 (20%) from MN group. There were 34 patients for evaluation in KC group, and 28 in MN group. Average age was 33.96 ± 6.93 years for KC group and 31.56±7.99 for MN group.

In 23 cases there was vaginitis by Candida albicans; in 18, it was mixed vaginitis and in 21, bacterial vaginosis. Distribution in different treatment groups is shown in table 1.

Table 1. Distribution in the different treatment groups

	Ketoconazole / clindamycin	*Metronidazole / nystatin*
Candida vaginitis	12	11
Bacterial Vaginosis	9	12
Mixed Vaginitis	13	5

Candida vaginitis

Candida albicans was cultured in vaginal discharges from 23 patients; however, it was not associated with any bacteria. Twelve cases belonged to the ketoconazol/ clindamycin group, and 11 to the metronidazole/ nystatin group. As regards symptoms, itching was found in 11/ 12 cases in KC group and 9/11 MN group; abnormal genital runoff was expressed in all the patients.

At the end of the study, culture for *Candida* was negative in 8/ 12 cases in KC group (66.7%) and in 6/11 in MN (54.5%) (p=0.68).

Itching disappeared in 8/ 11 cases (72.72 %) and 5/9 (55.5 %) (p=0,642) for KC and MN groups, respectively.

Although abnormal genital runoff remained in most patients, its appearance changed.

Mixed Vaginitis

Eighteen cases had mixed vaginitis, 13 in the ketoconazole/clindamycin group and 5 in the metronidazole/nystatin group. In almost all cases, there was a relationship of *Candida albicans* with *G. vaginalis*, *Mobiluncus* or other anaerobic bacteria.

Symptoms included itching and yellowish, unpleasant odor abnormal genital runoff for the 13 cases of KC group and the 5 cases of MN group.

At the end of the study, culture was negative for organism cultured initially in 11/13 patients in group KC (83.3%). *Mobilluncus* was cultured on day seven in the case where it was not considered bacteriological cure. The five cases of MN Group had

negative cultures (p = 0.500) with Fisher's exact test. Itching was cured in 11/13 cases in KC group and in 5 cases in the MN group. With respect to abnormal genital runoff, smell disappeared and changed its characteristics.

Bacterial Vaginosis

In 21 patients, bacteria were isolated as causative agents of vaginal infection, 9 patients in the ketoconazole / clindamycin group and 12 in the metronidazole / nystatin group. The germs isolated are shown in table 2.

Table 2. Isolated Germs

Isolated Microorganism	*Ketoconazole /clindamycin*	*Metronidazole /nystatin*
G. vaginalis	3	5
Mobilluncus spp.	3	6
Other anaerobes	5	6

Itching was found in 9/9 cases of KC group and in 10/12 of MN group, respectively; abnormal genital runoff was registered in all cases.

Culture negativization in KC group at the end of treatment was observed in 719 patients (77%). It was positive in two cases, one with *G. vaginalis* and another with *Mobiluncus*. In MN group, 8/12 (66.6 %) of cultures were negative in the same evaluation period (p = 0.470).

Itching disappeared in 5/9 (55.55%) patients of KC group and 6/10 (60.0%) of MN group (p = 0.605); abnormal genital runoff changed its characteristics and odor dissipated.

Overall study results for each group are summarized in table 3.

Table 3. Overall results by treatment group

Chi-square test.

It is noteworthy that most patients had dysuria, in addition to vaginitis characteristic symptoms.

None of the patients experienced adverse effects related to the treatment.

CONCLUSION

The results observed in the study show higher microbiological cure in the group receiving ketoconazole and clindamycin (76.47%) than in the group treated with metronizadole and nystatin (67.85%). From the clinical point of view, symptoms improved in a higher ratio for the combination ketoconazole/clindamycin (72.72%) than for metronidazole/ nystatin (66.6%). Although there was no statistically significant difference, there was a tendency toward improvement in the group that received ketoconazole/clindamycin; this lack of significance may be the result of an effect of sample size. Therefore, it is necessary to increase the number of subjects for future assessment studies.

Vaginal treatment with ketoconazole 400 mg and clindamycin 100 mg, every 24 hours over a period of six days for Candida vaginitis, bacterial vaginosis or both, offers clinical and microbiological cure statistically similar to the combination of metronidazole / nystatin. No adverse effects were found in any of the two groups, and medications were well tolerated by patients.

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The breech fetal pole has a large diameter o bitrochanteric diameter measuring 9 centimeters;
A small anteroposterior diameter, which measures 55 millimeters.
In the complete breech, fetal projectile dimensions are more significant: sacrotibial diameter (bent legs) is 12 centimeters, and 9 cm after ballottement.

Reprinted from: Fabre. Manual de Obstetricia [Obstetrics Manual]. Barcelona: Salvat Editores, 1941 ;p:113.