Randomized, single-blinded comparison of efficacy, safety and tolerability of metronidazole 750mg-miconazole 200mg vaginal suppository vs. metronidazole 500mg-nystatin 100,000 IU vaginal suppository in the treatment of bacterial vaginosis, vulvovaginal candidiasis, trichomoniasis, and mixed vaginal infections*

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ABSTRACT

Objective: This randomized, single-blind, two-arm controlled study compared the efficacy, safety, and tolerability of an intravaginal suppository preparation containing metronidazole 750mg + miconazole 200mg (Neopenotran Forte) with another vaginal preparation containing metronidazole 500 mg + nystatin 10000 IU (Flagystatin) in the treatment of bacterial vaginosis (BV), candidal and trichomonial vulvovaginitis (CVV, TV), mixed vaginitis and in the prevention of secondary candidal vulvovaginitis.

Materials and Methods: Women ages 18-45 years with chief complaints of abnormal vaginal discharge or vaginal/vulvar itching were examined and microbiologic confirmation of BV, VVC, TV or mixed infection was made. They were then randomly assigned to receive either treatment once daily (nightly) for 7 days. A total of 261 subjects had evaluable clinical and microbiological findings at the end of the study. Test of cure by Amsel criteria and Nugent score were performed twice after treatment.

Results: The overall test revealed that microbiological cure rate is significantly different between the two treatment groups.

Conclusion: The odds of being cured microbiologically is 2.35 times more in the metronidazole 750mg + miconazole nitrate 200mg group compared to the metronidazole 500 mg + nystatin 10000 IU group. However, no significant difference in the clinical cure between the two groups was found. Both drugs are safe and convenient to use.

Keywords: Bacterial vaginosis, vulvovaginal candidiasis, trichomonal vaginitis, mixed vaginal infections, metronidazole - miconazole vaginal suppositories, metronidazole 500 - nystatin vaginal suppositories

INTRODUCTION

Women of different ages see their physicians for a variety of symptoms and among the top reasons for gynecologic consult is an abnormal vaginal discharge. As much as therapies have been studied to treat a variety of vaginal infections or abnormal vaginal discharge, recommendation-giving bodies also have established different therapeutic regimens for vaginitis. Mono or combination therapy which can be administered locally or systemically may be used in the management of different forms of vaginitis.[1,2,3,4,5] Local and systemic treatments are both acceptable options however both routes of administrations have strengths and weaknesses. Oral regimens may need longer duration of treatment and may cause systemic adverse effects. Local treatment on the other hand may be highly favourable for patient compliance while at the same time providing short- and long-term cure. Optimal patient compliance is very important to obtain the maximum benefit from any form of vaginitis therapy.

Due to the changing life standards and the many requests from physicians and patients, the "Forte" form of the metronidazole - miconazole vaginal suppository was formulated, which allows once daily application to provide an alternative for both physicians and patients. Insertion of one metronidazole 750mg - miconazole 200mg vaginal suppository high into the vagina at night for 7 days is advised. In recurrent cases, or when the vaginitis has been resistant to other treatments, metronidazole 750mg - miconazole 200mg should be applied for 14 days. Insertion of metronidazole 750mg - miconazole 200mg vaginal suppository once daily is simple, easy-going and comfortable in all women, especially in working

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or travelling women.[6,7] It may also help solve a common problem, i.e. low compliance which decreases clinical success rate in vaginitis therapy.[7] Currently, there are no formal studies done on vaginitis and their treatment in the local setting. However research done in other countries showed that recurrent infections could also result in some psychological distress among 36% of patients suffering from recurrent vaginal infections. [8]

The objective of this study is to compare the efficacy, safety and tolerability of metronidazole 750mg - miconazole 200mg (Neopenotran Forte) vaginal suppositories and metronidazole 500 mg - nystatin 100,000 IU (Flagystatin) vaginal suppositories in the treatment of bacterial vaginosis (BV), vulvovaginal candidiasis (VVC) , trichomonal vaginitis (TV), and mixed vaginitis. Flagystatin vaginal suppository (Metronidazole 500 mg, Nystatin 100,000 IU) is also used for treatment of mixed infectious vaginitis, trichomonal vaginitis, monilial vaginitis and other fungal infections.[9]

MATERIALS AND METHODS

This study enrolled 309 women with chief complaints of abnormal vaginal discharge or vaginal/vulvar itching who consulted at the UP-PGH Department of Obstetrics and Gynecology Out Patient Department after protocol approval from the institutional technical and ethical review board. This study was registered with the UP-PGH Research Implementation and Development Office.

Inclusion criteria were the following:

1. 18-45 years old
2. Willing to abstain from alcohol intake during the study period
3. Willing to abstain from sexual intercourse during the therapy period and she and her partner should use the condom from end of therapy to visit 3 (90-95 days)

Exclusion criteria on the other hand were the following:

1. Patients on steroid therapy, on hormonal treatment or intrauterine device within one month.
2. Patients with genital warts, or other genital lesions
3. Patients who are to undergo vaginal surgery during the study period
4. Pregnant patients
5. Patients with STIs other than trichomoniasis
6. Patients who are hypersensitive to any of the study drug components
7. Patients who have systemic disorders like liver dysfunction, or hematopoietic disorders.
8. Patients with recurrent vaginitis

The subjects' demographics and their medical history were obtained after securing written consent from participants. Appropriate medical and internal examinations were done for each patient and samples were taken for microbiologic study. Allocation concealment was done through randomized treatment allocation using a randomization table generated by a computer programme.

The subjects were randomized into 2 groups: 158 women received metronidazole 750mg - miconazole 200mg vaginal suppository while 151 received metronidazole 500 mg - nystatin 100,000 IU vaginal suppository.

At visit 1 or at baseline evaluation, clinical history was taken, vaginal/pelvic examination was performed and samples of vaginal fluid taken. The patients were prescribed the medication according to a randomization table generated by a computer program to either metronidazole 750mg - miconazole 200mg vaginal suppository or metronidazole 500 mg - nystatin 100,000 IU vaginal suppository if indicated. The patients were instructed to insert the medications high into the vagina once daily (nightly) for 7 consecutive days. Specific procedures such as vaginal discharge identification, pH measurement, test for volatile amine ("whiff test") and identification of buds and hyphal elements, identification of motile trichomonads, and clue cells were done. Cultures for T. vaginalis and candidal organisms were obtained. Clinical diagnosis of BV was made if all of the following 3 criteria were present using Amsel's criteria. A Gram stain diagnosis of BV was made using Nugent's scoring scale. Symptomatic diagnosis of BV was made if total score is ≥ 7 using a symptom score. A clinical diagnosis of VVC was also made if total score is ≥ 7 using a symptom score. For clinical (symptomatic) diagnosis of TV, a clinical (symptomatic) diagnosis of TV was made if total score is ≥ 7 using a symptom score. For microbiological diagnosis of TV, a microbiological diagnosis was made by wet mount and culture.

Subjects were asked to come back for repeat gynaecological and microbiological examination after 7 days of treatment. The symptoms of vaginitis were recorded with grading of absent, mild, moderate or severe for BV, TV and VVC separately. A gynecological examination was performed and microbiological sample was taken at the same time. A second post treatment evaluation was done after 3 months.

Subjects were evaluated in terms of a) clinical cure as defined by composite signs/symptoms score < 7. Time to symptom relief was assessed by direct questioning at the 3, 5-6, 8-10 days via phone calls and b) microbiological, therapeutic cure & failure to reveal recurrence rates. They were also assessed for presence of symptomatic secondary vulvovaginal candidiasis secondary to BV treatment. For efficacy assessment: for bacterial vaginosis, clinical cure was defined by the absence of all clinical

criteria at 2nd visit. A clinical cure was defined as follows: whiff test was negative for amine odor, clue cells < 20% on wet mount exam, vaginal pH is ≤ 4.5, using pH paper that measures from 4.0 to 6.0. In addition to clinical cure, a microbiological cure was defined as a Nugent gram stain score < 4 or 4-6 with Clue cells < 20% on wet mount exam. For vulvovaginal candidiasis, microbiologic cure was defined as less than 10 colonies per plate. For trichomonal vaginitis, negative culture was evaluated as a microbiologic cure. For mixed vaginal infections, clinical (symptomatic) cure was assessed for each pathogen which caused mixed vaginal infections. Microbiologic cure was also assessed for each pathogen.

To evaluate severity of symptom, symptoms were recorded with grading of absent, mild, moderate or severe (score of 0-3 for each symptom, for a total symptom score ranging from 0-no symptoms to 15-all severe symptoms). Subjects who were asymptomatic or whose composite score was <7 at baseline visit were classified as non-evaluable. Time to symptom relief was assessed by direct questioning at the 3, 5-6, 8-10 days via phone calls.

To compare if clinical and microbiological cure is significantly different between the two treatment groups considering the cure rate across visits 2 and visit 3, an overall test was performed using the generalized estimating equations test (GEE).

Safety was determined by physical examination, monitoring for untoward side effects via subject and investigator observations, subject interviews, and reports of any adverse experience throughout the course of the study. Safety was determined at day 3, 5-6, 8-10 via telephone calls and by physical examination at 2nd visit.

Analysis was performed on an intention to treat (ITT) and per protocol basis. ITT patients included those who were enrolled and randomized to the treatment groups and have used at least one treatment but deviated from the study protocol. For the per protocol analysis, these patients were excluded.

Baseline and key characteristics were compared according to treatment groups. Qualitative data was analyzed using Chi-square test and Fisher's exact test where appropriate and relative risks (with 95% confidence limits) were calculated. Quantitative data were compared using a Student's t-test, or Mann-Whitney U-test if assumptions of the parametric test were not satisfied. Statistical analyses was performed using STATA.

RESULTS

Out of 309 women enrolled only 261 women were evaluated for efficacy (135 for metronidazole 750mg - miconazole 200mg and 126 for metronidazole 500 mg - nystatin 100,000 IU). The attrition rate was not significant between metronidazole 750mg - miconazole 200mg and metronidazole 500mg - nystatin 100,000 IU (p = 0.771). Table 1 summarizes the attrition and study populations.

Tables 2 and 3 present the clinical and microbiological diagnosis of the 309 subjects enrolled in the study. More than half (58.58%) of the enrolled subjects had clinical and microbiological diagnosis of bacterial vaginosis while a third of the subjects (30.10%) had vulvovaginal candidiasis. Very few subjects had trichomonal vaginitis (1.29 %) and mixed vaginal infections (9.7%).

Categorical subject variables were summarized as frequency and percentages of total within each treatment group. There were no significant differences on baseline

Table 1. Disposition of Subjects

Disposition	Metronidazole 750mg - Miconazole 200mg	Metronidazole 500 mg - Nystatin 100,000 IU	Total	p-value
Screen failure	34 (17.71%)	28 (15.64%)	62	
Completed	135 (70.31%)	126 (70.39%)	261	0.771
Lost to follow- up	23 (11.98%)	25 (13.97%)	48	
TOTAL	192	179	371	

Table 2. Clinical Diagnosis (for All Enrolled Subjects)

Clinical Diagnosis	Metronidazole 750mg - Miconazole 200mg (n=158)	Metronidazole 500 mg - Nystatin 100,000 IU (n=151)	Total (n=309)
BV	91 (57.59%)	90 (59.60%)	181 (58.58%)
TV	2 (1.27%)	2 (1.32%)	4 (1.29%)
VVC	50 (31.65%)	43 (28.48%)	93 (30.10%)
Mixed (BV + TV)	2 (1.27%)	2 (1.32%)	4 (1.29%)
Mixed (BV + VVC)	11 (6.96%)	14 (9.27%)	25 (8.09%)
Mixed (TV + VVC)	1 (0.63%)	0	1 (0.32%)
No Answer	1 (0.63%)	0	1 (0.32%)

Table 3. Microbiological Diagnosis (for All Enrolled Subjects)

Microbiological	Metronidazole 750mg - Miconazole 200mg	Metronidazole 500 mg - Nystatin 100,000 IU	Total
BV	78 (49.37%)	78 (51.66%)	156 (50.49%)
TV	2 (1.27%)	1 (0.66%)	3 (0.97%)
VVC	60 (37.97%)	60 (39.74%)	120 (38.83%)
Mixed (BV + TV)	2 (1.27%)	3 (1.99%)	5 (1.62%)
Mixed (BV + VVC)	16 (10.13%)	8 (5.3%)	24 (7.77%)
No answer	0	1 (0.66%)	1 (0.32%)

demographic and clinical characteristics between subjects randomized to metronidazole 750mg - miconazole 200mg vs. metronidazole 500mg - nystatin 100,000 IU.

Efficacy Analysis

Changes in Efficacy Measures During the Study

Table 4 shows the comparison of the clinical and microbiological cure between metronidazole 750mg - miconazole 200mg and metronidazole 500mg - nystatin 100,000 IU treatment groups at each post-treatment visit. The metronidazole 500mg - nystatin 100,000 IU group has a significantly lower microbiological cure rate when compared with the metronidazole 750mg - miconazole 200mg ($p = 0.027$). This was observed on the 3rd visit. This signifies that the odds of being cured is 2.35 times more in the metronidazole 750mg - miconazole 200mg group compared to the metronidazole 500mg - nystatin 100,000 IU group ($p= 0.017$).

As shown in Table 4, the cure rates as regard to microbiological and clinical rates were not statistically different for both groups at visits 2 and 3, except for a better microbiological cure for the metronidazole-miconazole group at visit 3. At visit 3, there was significant difference in terms of microbiological cure in favor of the metronidazole-miconazole group ($p = 0.027$).

The prevalence rate for BV in this study is 58.6%, for VVC the rate is 30.1%, and for TV, prevalence is 1.3% and these rates are consistent with other studies (Table 2).

Table 5 shows the overall test and revealed that microbiological cure rate is significantly different between the two treatment groups ($p = 0.017$). The odds of being cured is 2.35 times more in the metronidazole 750mg -

Table 4. Clinical and Microbiological Cure (Visit 2 and Visit 3 Post Treatment)

	Metronidazole 750mg - Miconazole 200mg (n = 145	Metronidazole 500 mg - Nystatin 100,000 IU (n = 137)	Total (n = 282)	p value
Clinical Cure (2nd visit)				
Yes	131 (90.34%)	121 (88.32%)	252 (89.36%)	0.582
No	14 (9.66%)	16 (11.68%)	30 (10.64%)	
Clinical Cure (3rd visit)				
Yes	129 (88.97%)	116 (84.67%)	245 (86.88%)	0.286
No	16 (11.03%)	21 (15.33%)	37 (13.12%)	
Microbiological Cure (2nd visit)				
Yes	136 (93.79%)	120 (87.59%)	256 (90.78%)	0.072
No	9 (6.21%)	17 (12.41%)	26 (9.22%)	
Microbiological Cure (3rd visit)				
Yes	137 (94.48%)	119 (86.86%)	256 (90.78%)	0.027
No	8 (5.52%)	18 (13.14%)	26 (9.22%)	

Table 5. Overall Test for the Clinical and Microbiological Cure (Visit 2 and Visit 3 Post Treatment)

	Odds Ratio	95% CI	P value
Clinical Cure	1.35	0.73-2.52	0.340
Microbio-logical cure	2.35	1.17-4.74	0.017

miconazole 200mg group compared to the metronidazole 500mg - nystatin 100,000 IU group. However, no significant difference on the clinical cure between the two groups was found (p=0.340).

Regarding tolerability, the subjects for both treatment groups stated that treatment use was generally very acceptable in terms of its ease of insertion, convenience of dosage regimen, and presence/absence of irritation on insertion. However, there were 2 subjects who indicated that metronidazole 500mg - nystatin 100,000 IU is not acceptable based on the criterion on presence/absence of irritation on insertion.

DISCUSSION

It is incumbent for a physician to manage the different types of vaginitis appropriately. Bacterial vaginosis (BV) is the most common cause of vaginal discharge among women of reproductive age and accounts for about 40-50% of all cases.[10,11,12] There is absence of inflammation in BV and as such the term is vaginosis rather than vaginitis.[12] On the other hand, vulvovaginal candidiasis (VVC) is typically a disease characterized by signs and symptoms of inflammation caused by Candida species. And after BV, it is the second most common vaginitis that occurs in about one-third of women.[11] Clinically, diagnosis is based on what the patient actually experiences and not on identification of fungal species on microscopy or culture.[7,11] Trichomoniasis is sexually transmitted among the three vaginitis. The organism infects initially the squamous epithelium in the female urogenital tract. Sexual transmission is the only known mode of transfer and fomites have no role in active transmission. Trichomoniasis often coexists with BV in as much as 60-80% [11,13]. Diagnosis is usually based on clinical findings and expertise of the physician.[7] Various guidelines recommend different diagnostic tests for each vaginitis, however, simple office microscopy may be sufficient in making an accurate diagnosis.[1,3,5,11] Sensitivity differs according to the experience of the performer. A more practical approach is the use of the pH paper (litmus). A value of beyond 4.5 is indicative of Trichomonas infection or BV with sensitivity of 84-97% and specificity of 57-78%. False positive results are due to recent sexual activity, douching, cervical mucus, and presence of blood. BV often yield pH of 5.0-6.0, trichomoniasis a pH of 5.0-7.0, and candidiasis often result with normal pH of less than 7.0.[1,3,11] Women presenting at the clinics with signs and symptoms of abnormal vaginal discharge should also undergo careful pelvic examination to rule out malignancy wherein biopsy and colposcopy are indicated.

This study showed that the most prevalent vaginitis in the study setting was BV with 58.58% of subjects having BV and 30.10% having VVC. Only 1.29% had TV. The most common combination mixed infection was BV + VVC (8.09%) followed by BV + TV (1.29%), and the least was TV + VVC (0.32%). The local incidence in this study reflects prevalence rates in other countries wherein BV accounts for around 40-50% of cases. Globally VVC comes next in prevalence and it was also reflected in this study. TV infection being a sexually transmitted disease comes in with least diagnosis. Among the mixed diagnosis of vaginitis, the most common reflected diagnosis was BV + VVC and this also is seen in other researches, although trichomonal infection also occurs with bacterial vaginosis in as much as 60-80%. [1,3,7,11,13]

The objective of this study was to compare the efficacy, safety and tolerability of two vaginal suppositories - metronidazole 750mg - miconazole 200mg and metronidazole 500 mg - nystatin 100,000 IU in the treatment of bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), trichomonal vaginitis (TV), and mixed vaginitis. Both study products showed no statistically significant differences for clinical cure at visits 2 (21-30 days) and 3 (90-95 days) for all diagnoses. There was an overall cure rate of 90.34% at visit 2 and 88.97% at visit 3 for the metronidazole 750mg - miconazole 200mg group. This confirms previous studies done on combination of metronidazole-miconazole in women with vaginitis wherein very high cure rates were obtained for all vaginitis including mixed infection [7, 14, 15]

In the present study the microbiological cure rate at visit 2 was slightly better for metronidazole 750mg - miconazole 200mg group compared to metronidazole 500mg - nystatin 100,000 IU group (93.79% vs. 87.59%, p = 0.72). This means that for short-term cure, the metronidazole-miconazole combination drug is more efficacious than with metronidazole-nystatin formulation.

Significant microbiological cure was attained with the metronidazole-miconazole group compared with the metronidazole-nystatin group, and one is 2.35 times more likely to get cure using the metronidazole-miconazole suppository compared to the other drug.

This combination topical therapy was better in eradicating pathogenic vaginal organisms at long-term periods of up to 3 months. Monotherapy with metronidazole on one hand, has lower long-term cure rates owing to the lack of synergism with another azole drug.[6] This is consistent with other published studies done globally that showed that metronidazole 750mg -

miconazole 200mg has microbiological cure rate of 81% to 97% for all 3 vaginitis and including mixed vaginitis.[7,14,15] Clearly, this is one advantage of using 2 topical azole drugs in eradication and suppression of anaerobic, fungal organisms and even trichomonas protozoa.

There are numerous therapies described in literature for management of the different vaginitis.[1,3,4,5,16] Varied results are seen when comparing efficacy and tolerability of oral and topical preparations of either mono or combination therapies. A Cochrane systematic review involving twenty-four trials with 4422 participants demonstrated that clindamycin preparations, oral metronidazole, and oral and intravaginal combination tablets were effective for treating BV.[17] Another study comparing efficacy of topical and oral metronidazole showed that efficacy of topical form was similar to oral metronidazole and that there were fewer gastrointestinal side effects with the topical form of treatment.[18] A systematic review in 1995 on the use of topical metronidazole for BV showed that of eight formulations of topical metronidazole, use of three day preparation was more effective than one-day regimens. The high dose (1000mg) 3-day sponge was found to have a better cure rate than the lower dose (250mg) 3-day sponge (88% vs. 56%).[19]

For metronidazole use in trichomoniasis, a Cochrane meta-analysis showed that nitro-imidazoles are highly effective in treatment of this infection among 54 studies that were included in the review.[20] Resistance to oral metronidazole though, has been a problem since 1962. Lossick and Kent estimated that marginal resistance occurred in 1 of every 50-75 cases, low to moderate resistance occurred in 1 of 200-400 cases, and very-high-level resistance occurred in 1 of 2000-3000 cases.[21] These studies suggest that oral metronidazole continues to have good overall clinical efficacy but metronidazole-resistant Trichomonas may pose a therapeutic challenge. As such various studies have been done with use of topical metronidazole in Trichomonas vaginalis (TV) infection.[21,22,23] The bioavailability of metronidazole is dependent on the route of administration. Oral and IV metronidazole has a bioavailability of 93 to 100% while vaginal absorption of the drug is lower. Vaginally administered metronidazole is also much slower to achieve peak concentration in the plasma, taking 9-16 times longer than an oral dose. However, absorption of metronidazole in the vagina is dependent on a number of factors, including drug formulation (insert or cream), dose, and physicochemical characteristics of the vagina during treatment. These variables may explain why some women respond better to vaginal treatment with metronidazole than others.[22]

For VVC, the CDC recommends as first line of therapy topically administered azoles or oral fluconazole.[1] Again, patient preference should be elicited as some women prefer vaginal preparations than oral antifungal drugs.[7] Reef et al. recommended that topical anti-fungal treatments should be the first line of management, but mentioned that better compliance might be achieved with oral agents.[23]

For mixed vaginitis, Ozyurt et al. demonstrated in their study that combination vaginal pessary containing metronidazole 500mg and 100mg miconazole among 97 women with microbiological and clinical diagnosis of either BV, TV, VVC, or mixed vaginitis was both efficacious and safe. The dosing regimen used was twice daily vaginal insertion for seven days. Results showed vaginitis resolution in 91% of the 74 patients evaluated. The overall microbiological cure rate for mixed vaginitis was 86% and the authors concluded that the pessary combination provides immediate and effective treatment for vaginitis.[7]

The advantage of combining metronidazole and miconazole in one topical product has been pharmacologically elucidated. Metronidazole is believed to act on four phases of cell cycle. Formation of redox intermediate intracellular metabolites is key in its bacterial killing effect. On one hand, miconazole's mode of action involves its ability to increase cell membrane permeability with loss of ergosterol biosynthesis and interaction with phospholipids, and possibly inhibiting uptake of precursors of RNA and DNA.[6] While there are no direct studies proving either synergism or antagonism of the 2 azole drugs, various studies on treatment of different vaginal infections have long since proved its efficacy and high tolerability. Reported cure rates of miconazole when combined with metronidazole, range from 81.0% to 84.4%.[13,14,15,16] Our results are consistent with literature that the use of combination azole therapy as single application daily for 7 consecutive days resulted in remarkable improvement in signs and symptoms of vaginitis. Miconazole, as antifungal drug, may also inhibit development of secondary vaginal candidiasis.[24]

There are also studies done on metronidazole-nystatin combination therapy and results were promising. In a study done and published in 2004 by Sanchez and co-workers, it was shown that metronidazole-nystatin was significantly more effective than metronidazole gel alone in the treatment of BV.[25]

The vaginal ovules under study contain 750mg of metronidazole and 200mg of miconazole. Various literature documents the efficacy and safety of this preparation. Morton in 1993 demonstrated that this preparation achieved a microbiological cure rate of 83% with overall clinical resolution of 73%.[14] In a subsequent study conducted by Kukner S et al in 1996, the same formulation showed efficacy rates of 80% for trichomoniasis, 93.4% for BV and 84.4% for candidal vaginitis.[16] Ozyurt and co-workers in 2001 demonstrated microbiological cure rates

of 97.3% for Trichomonas infection, 86.6% for BV and 81% for candidal vaginitis with this preparation. Overall vaginitis symptoms improved in 91% of patient that were evaluated.[7] In this local study, there was an overall cure rate of 90.34% at visit 2 and 88.97% at visit 3 for the metronidazole 750mg - miconazole 200mg group.

Subjects in this study reported that therapy was generally acceptable in terms of ease of insertion, convenience of dosage regimen, and presence or absence of irritation. There were also no reports of any systemic side effects of headache, drowsiness, vomiting, metallic taste or tiredness. On practical points, women nowadays are considered as partners in care and are thus empowered to choose for themselves how treatment for their vaginal infections will be administered. As has been concluded in a study done by Sobel et al. in 1995, therapy of vaginitis should be individualized, taking into consideration disease severity, history of recurrent disease, and patient preference.[26] Primary care management of patients revealed that clinical decisions for minor health problems are made everyday and one of the more important issues includes patient preference in management of vaginitis, especially VVC.[27] In a survey among 96 women with BV, more women preferred clindamycin ovule and the results suggested that there is potential for improved compliance with topical forms of therapy.[28] Topical therapy also circumvents systemic side effects of oral forms of antimicrobial treatment. What is obviously a clear advantage is the avoidance of gastrointestinal side effects especially disulfiram-like reactions with oral antibiotics such as metronidazole.

CONCLUSION

In conclusion, metronidazole 750mg - miconazole 200mg suppositories represent a very effective and safe mode of therapy for BV, trichomoniasis, vaginal candidiasis, and mixed infections.

The two drugs studied are comparable. The metronidazole-miconazole vaginal suppository is more effective than the metronidazole-nystatin preparation in terms of long -term microbiological cure.

Both drugs are safe and convenient to use although more patients report more acceptability for metronidazole 750mg - miconazole 200mg suppository. The use of this formulation in once daily dosing at bedtime for seven days can help prevent persistent and recurrent infections.

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