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First Line Treatment and Relief of Bacterial Vaginosis-related Vaginal Complaints with Metronidazole and Multi-Gyn® ActiGel

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Abstract

Metronidazole has been the treatment of choice prescribed for bacterial vaginosis (BV). Interfering with the bacterial adhesion mechanism may offer an alternative. Multi-Gyn® ActiGel is a vaginal gel based on a high molecular polysaccharide complex that intervenes in microbial adhesion. During this open label study, 47 age-matched women with BV and related complaints received as first line treatment either a course of prescribed oral metronidazole or ActiGel intra-vaginally. Results: Oral metronidazole was slightly more effective at one week post treatment; ActiGel was equally as effective as metronidazole at three months post treatment. Conclusion: Physicians may encourage the use of this vaginal gel for self-care in order to treat and relieve BV related symptoms and thus reduce the prescription of antibiotics and the emergence of resistance.

Keywords

Bacterial vaginosis (BV), vaginal complaints, anti-adhesion, metronidazole, vaginal gel, Multi-Gyn® ActiGel, polysaccharides

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A healthy vagina is generally dominated by hydrogen-peroxide-producing lactobacilli which inhibit the growth of microorganisms such as *Gardnerella vaginalis* (*G. vaginalis*).¹ A depletion of lactobacilli and an over-colonisation of anaerobic bacteria such as *G. vaginalis*, *Bacteroides*, *beta-Streptococci*, *Mobiluncus/Falcivibrio*, *Prevotella bivia*, *Lachnospiraceae* and *Mycoplasma hominis* leads to a dysbacteriosis called bacterial vaginosis (BV).^{2–5} This is a prevalent vaginal disorder which affects many women of a reproductive age with an infection rate of 15–50 %. The condition is associated with complaints such as malodour of the discharge, excessive discharge, burning and itching. BV is associated with serious complications such as pelvic inflammatory disease, cervicitis, pre-term labour and an increased risk for acquiring sexually transmitted diseases.^{6–10}

Oral metronidazole is most frequently prescribed for the treatment of BV and is the treatment of choice recommended by the Centers for Disease Control and Prevention. Metronidazole results in a cure rate of 70–80 % at four weeks follow up. However, up to 40 % of the women treated with metronidazole for BV have a recurrent infection one to three months following treatment.^{11–13} One of the concerns, following the use of systemic metronidazole, are the potential adverse effects. These include: nausea, vomiting, anorexia, heartburn, headache, a metallic taste in the mouth and decrease of libido.¹⁴ Of concern is also the interaction with medication such as lithium and coumarines as well as the frequent occurrence of candida after a course of metronidazole.^{15,16}

The less-than-optimal cure rates, coupled with the high recurrence rates and the potential for adverse effects for oral metronidazole has prompted a search for an alternative therapy for the treatment of BV. The low pH of a normal microflora significantly increases the binding capacity of lactobacilli to vaginal epithelial cells. The adhesion of *G. vaginalis* to vaginal epithelial cells is also pH dependent and binds maximally at a pH between 5–6.¹⁷ Due to these properties, vaginal acidification has been examined as a means of treating BV, but has been shown to be ineffective in discouraging the growth of BV-associated micro-organisms, and in promoting vaginal re-colonisation with lactobacilli.¹⁸

In order to avoid clearance via urine flow and vaginal secretion, a pathogen must first adhere to host cells, thus adherence of anaerobic bacteria is a critical step for pathogenesis. A treatment aimed at preventing adherence of *G. vaginalis*, together with vaginal acidification, could increase clinical cure rate and decrease recurrence of BV. Multi-Gyn® ActiGel (ActiGel) is an acidic gel based on 2QR-complex. 2QR-complex is a negatively charged, high molecular, multi-branched polysaccharide complex that interferes with the adhesive mechanism of bacteria.¹⁹ This suggests the potential of ActiGel in BV and its related vaginal complaints. As an acid gel, ActiGel also maintains an optimal vaginal pH of 4.1. ActiGel is not an antiseptic or an antibiotic such as metronidazole and has no adverse effects.

The aim of this study was to compare the short and long term efficacy of metronidazole versus the over the counter (OTC) topical ActiGel in

an open label, randomised study for the treatment and relief of BV related vaginal complaints.

Materials and Methods

Forty-seven consenting age-matched women entered this open-label study, which was performed at a gynaecological practice Belgrade, Serbia. All of the women had experienced vaginal complaints during the previous year. Exclusion criteria for the study were pregnancy, hypersensitivity for metronidazole and vaginal bleeding of unknown origin. Diagnosis of BV was established based on the personal history and included the presence of at least three out of four Amsel criteria: increased vaginal discharge, elevated vaginal pH > 4.5, the presence of clue cells on microscopic examination and an amino odour after the addition of potassium hydroxide to the specimen.³ Although Nugent's score is a laboratory method with higher reproducibility, in daily clinical practice the Amsel criteria method is a convenient and inexpensive means of diagnosing and first line treatment of BV.^{20,21}

Patients were evaluated at presentation (week 0) and during two follow-up visits: one week (week 1) and 12 weeks post treatment (week 12). During each visit vaginal pH was measured using an indicator strip (Duotest, Macherey-Nagel, pH 3.5–6.8), Amsel criteria and vaginal complaints were noted by the clinician, and cell samples were collected following a pelvic examination. Vaginal complaints included: itch, pain, malodour and vaginal discharge and were assessed during each visit. Symptoms were categorised into a symptom score in which no symptoms = 0, mild symptoms = 1, moderate symptoms = 2 and severe symptoms = 3.

When entering the clinic, patients were alternately placed in the metronidazole group or the ActiGel group by the investigator. The even numbered patients (n=23) received 400 mg oral metronidazole every eight hours, three times a day for a period of seven days. The odd-numbered patients (n=24) received over the counter ActiGel intravaginally in the mornings and in the evenings for a period of five days. Patients in ActiGel group were given the option of terminating the use of ActiGel and receiving metronidazole instead. None of the women chose to do so.

Results

In this study 23 consenting women with an average age of 34 years received oral metronidazole treatment and 24 consenting women with an average age of 33 years received ActiGel vaginal gel for the treatment of BV. Statistical evaluation doesn't apply for the parameters of this number of patients and results were evaluated by the statistician with the use of percentages.

Average vaginal pH of 5.9 was reduced in both groups in week 1 to 4.5 and remained reduced to 4.5 in both groups in week 12. One week post-treatment all the women in the metronidazole group and 84 % of the women in the ActiGel group presented with less than three of the Amsel criteria. After 12 weeks, 83 % in the metronidazole group and 87 % of the women in the ActiGel group had less than three of the Amsel criteria.

Figure 1 presents the number of patients diagnosed with BV in the cytology, with itch (A), pain (B), malodour (C) and excessive discharge (D) complaints as established by the clinician. In regard to the itch symptom scores, at start 26 % of the women in the metronidazole group and 30 % in the ActiGel group did not experience itch (symptom

score 0). After one week treatment these percentages increased to 91 % (metronidazole) and 87 % (ActiGel group). In week 12 this was 78 % for the metronidazole patients and 79 % for the ActiGel patients. A reduction was also found for the pain symptom score in which at start 30 % of the women in the metronidazole group and 52 % in the ActiGel group did not experience pain (symptom score 0). After one week treatment these percentages increased to 96 % (metronidazole) and 78 % (ActiGel group). In week 12 this was 87 % for the metronidazole patients and 88 % for the ActiGel patients. In regard to malodour, at start 9 % of the women in the metronidazole group and 0 % in the ActiGel group did not experience malodour (symptom score 0). After one week treatment these percentages increased to 87 % (metronidazole) and 52 % (ActiGel group). This was 83 % for the metronidazole patients versus 70 % for the ActiGel patients, in week 12. Finally, upon examining the excessive discharge symptom score, at start 13 % of the women in the metronidazole group and 4 % in the ActiGel group did not experience excessive discharge (symptom score 0). After one week treatment these percentages increased to 87 % (metronidazole) and 48 % (ActiGel group). This was 83 % for the metronidazole patients versus 70 % for the ActiGel patients in week 12.

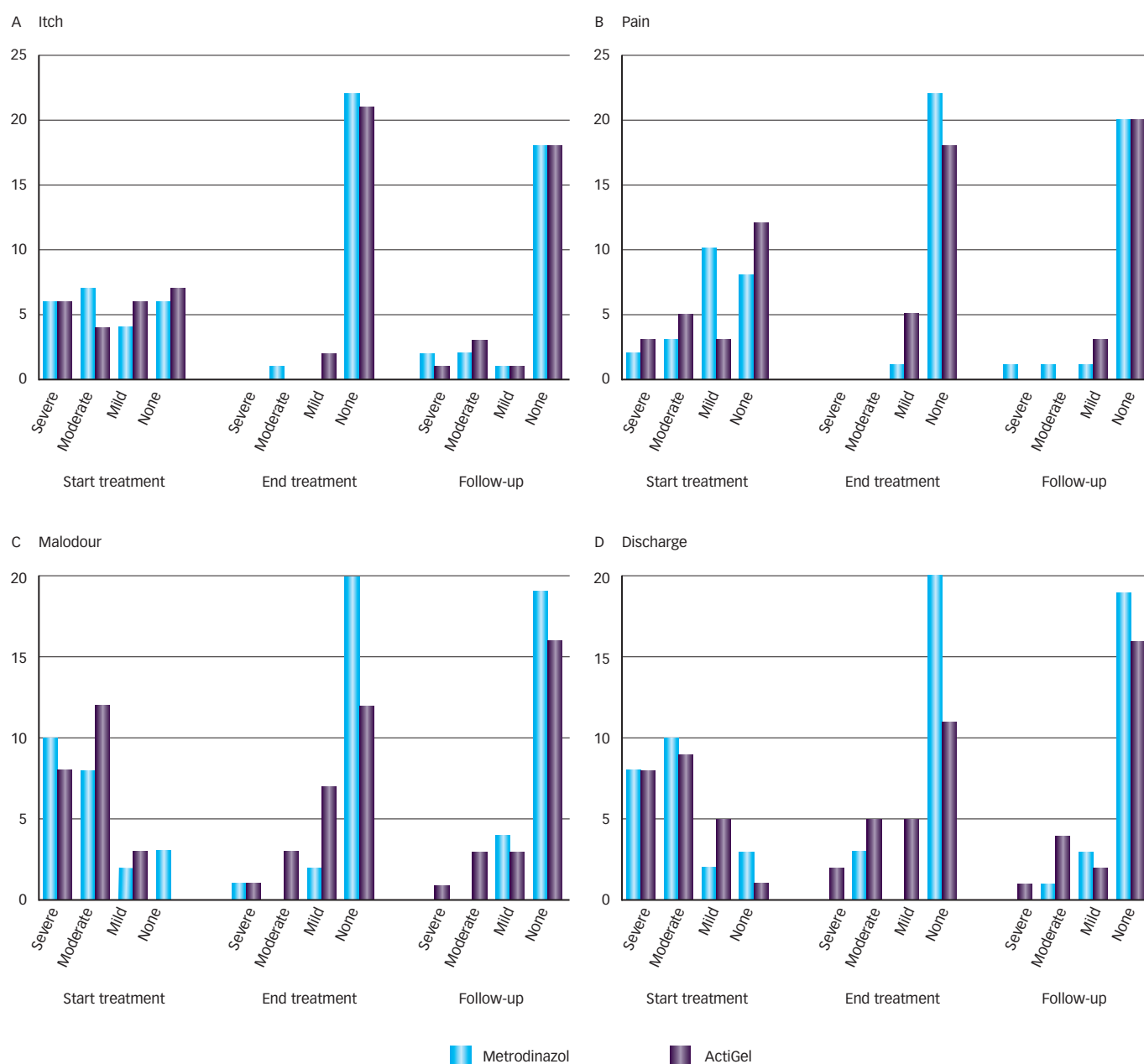
Discussion

To date, oral metronidazole has been the treatment of choice prescribed for BV. Alternative therapies have been examined due to the less-than-optimal cure rates, high recurrence rates and the potential adverse effects of oral metronidazole and particularly the frequent post-treatment occurrence of candida. Vaginal acidification has been examined as a means of treating BV, but the use of acidic vaginal gels has been shown to be controversial in discouraging the growth of BV-associated micro-organisms and in promoting vaginal re-colonisation with lactobacilli.^{18,22}

In order to examine the combination of vaginal acidification and prevention of adherence of *G. vaginalis* for the clinical cure a decrease in the recurrence of BV and its related complaints, we compared the efficacy of short- and long-term effects of the acidic vaginal gel ActiGel with 2QR-complex and its property to prevent adherence of *G. vaginalis* versus oral metronidazole in a randomised, open label study.

Vaginal pH was high for both groups at presentation and reduced in both groups one week and three months post treatment showing that vaginal pH restores in both groups. As in most first line consultancy practices, diagnosis of BV was based on the patient's complaints, personal history and the presence of at least three out of four Amsel criteria. When examining Amsel criteria and the symptom scores: pain, malodour and excessive discharge, all results improved more in the metronidazole group one week post treatment compared to the ActiGel group. However, three months post treatment an equal reduction in Amsel criteria, pain-, malodour- and excessive discharge- symptom scores was obtained for both the metronidazole and the ActiGel group. The symptom score for itch was reduced equally in the ActiGel group when compared to metronidazole for both follow-up visits.

Taken together these results imply that though oral metronidazole is somewhat more effective one week post treatment, these results show that equal results are obtained three months post treatment. The Amsel criteria nor the symptom scores reached a 100 % cure rate for the metronidazole or the ActiGel group one week and three month post treatment implying that these patients were not yet

Figure 1: Number of Patients Diagnosed with Bacterial Vaginosis in the Cytology with Itch (A), Pain (B), Malodour (C) and Excessive Discharge (D)

Complaints as established by the clinician. Left in week 0, middle in week 1 and right in week 12.

completely cured and should be treated further. The effectiveness of the ActiGel can be attributed to its main component: 2QR-complex, which consists of a negatively charged, high molecular, multi-branched polysaccharide complex derived from Aloe vera. A previous study has shown that these polysaccharides have a potent anti-adhesive effect against *Helicobacter pylori* by physically inhibiting their adherence to gastric cells *in vitro*.²³ Preventing adherence of *G. vaginalis* could prevent infection and the formation of a biofilm. Microscopic analysis of vaginal biopsies of women with BV has revealed the presence of a bacterial biofilm on the vaginal epithelial cells.²⁴ Biofilm formation is an important virulence factor as the presence of a biofilm is correlated to increased antibiotic tolerance and resistance to host immune defences.²⁵ As adherence is the first step in the formation of a biofilm, a treatment aimed at adherence inhibition could increase clinical cure rate and recurrence of BV.

These results are confirmed by this study in which long term analysis shows that ActiGel is as effective as metronidazole. Moreover, patients were equally satisfied with both treatments for the relief and treatment of their vaginal complaints.

Conclusions

The promising results of this study suggests that ActiGel with anti-adhesive polysaccharides that neutralise pathogens by interfering with adhesion mechanism offers an alternative pathway to antibiotic intervention as a first line treatment for BV and related symptoms. Further studies with larger patient groups are warranted. However, physicians may already start to encourage the use of this non-toxic OTC gel for self-care in order to treat as well as prevent recurrence of BV and thus reduce the prescription of antibiotics and emergence of resistance. ■

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