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Successful treatment of bacterial vaginosis with a policarbophil-carbopol acidic vaginal gel: results from a randomised double-blind, placebo-controlled trial

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Abstract

Objective: We evaluated the efficacy of a mucoadhesive vaginal gel (MVG, Miphil©) with acidic-buffering properties in bacterial vaginosis (BV).
Study design: Double-blind, placebo-controlled, 12-week trial.
Subjects: A total of 45 non-pregnant women with BV were enrolled in the trial. Patients were treated with MVG 2.5 g or the corresponding placebo (P) daily for the first week and then every 3 days for the following 5 weeks (treatment phase) in a 2:1 ratio. All patients were followed for an additional 6 weeks without treatments (follow-up phase). Clinical cure was defined as absence of vaginal discharge, vaginal pH <4.5, a negative fish odour test and a Nugent score <7.
Results: At week 6, 28 out of 30 women (93%) in the MVG group were clinically cured in comparison with only 1 out of 15 (6%) in the P group ($P = 0.0001$). At week 12, 86% of MVG treated women remained cured in comparison with 8% in P group ($P = 0.0001$). At baseline, the vaginal pH was 6.1 ± 0.7 in the MVG and 5.5 ± 0.7 in the P group. Vaginal pH significantly ($P = 0.003$) decreased to 4.3 ± 0.3 in the MVG group. In P group non-significant modifications of vaginal pH were observed (5.1 ± 0.5).
Conclusion: Our results demonstrated that this MVG is an effective treatment of BV.

Keywords: Bacterial vaginosis; Acidic buffering vaginal gel; Randomised controlled trial

1. Introduction

Bacterial vaginosis (BV) is the most common cause of leucorrhoea in women [1]. Its prevalence ranges from 17 to 40%, depending on the population studied [2]. BV is considered an important risk factor for obstetric complications such as preterm birth, low birth weight and post-partum endometritis [3]. Metronidazole and clindamycin are considered effective treatments [4]. The recurrence rate of BV remains high despite adequate chemotherapy treatment. With metronidazole, 30% of patients experienced recurrence of BV symptoms within 3 months [5]. Clindamycin treatment is associated with a recurrence rate of 25% after 28 days [6]. A persistent high (i.e. >4.7) vaginal pH is a common alteration found in patients with recurrence of BV after effective therapy [7]. Therefore, in BV, a failure in vaginal pH normalisation after antibiotic therapy could promote recurrences. Miphil™ (Mipharm, Italy) is a mucoadhesive vaginal gel (MVG) formed by two polymers, polycarbophil and carbophol, able to reduce vaginal pH. Polycarbophil, a weak polyacid, is a large molecule that it is able to stick on the vaginal epithelial cells until they turnover, up to 3–5 days, and buffers the vaginal secretions near its pK_a (i.e. 4.3). In women with suspected BV [8] the MVG

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has demonstrated an ability to reduce the vaginal pH from 5.4 to 4.6. So far no clinical data were available regarding the clinical efficacy of MVG in the treatment of BV.

2. Study aims

To evaluate the efficacy and safety of MVG in the treatment of BV in non-pregnant women in comparison with placebo.

3. Study outcomes

The primary study outcome was to compare the clinical and laboratory cure rate between the two groups at week 6 (end of treatment phase) and at week 12 (end of follow-up phase). Secondary outcomes were to compare the effects on vaginal pH and the vaginal pH normalisation rate. Clinical cure rate was defined as the disappearance of the following signs and symptoms of BV: homogenous vaginal discharge; presence of ≥ 2 or more clue cells at the wet mount microscopy; a Nugent score >7, a vaginal pH >4.7 and a positive Whiff test. Normalisation of vaginal pH was defined as the percentage of women with a vaginal pH <4.6.

4. Patients and methods

The study was a double-blind, prospective, randomised, parallel groups, placebo-controlled trial. A primary Gynaecology Ambulatory Clinics took part in this trial. Major inclusion criteria were: age between 20 and 75 years and a confirmed diagnosis of BV according to the Amsel criteria and a Nugent score >7. Women were excluded from entry into the study if they were pregnant or had received topic, antifungal or antibiotic therapy within the past 2 weeks. The study protocol was approved by the local Institutional Review Board. A total of 45 women with BV were enrolled in the study, after their informed consent. Randomisation was performed using a computer-generated randomisation list (Arcus Quickstat, Cambridge, UK) with a block of four patients in a 2:1 ratio. BV was diagnosed according to the presence of at least three out of four of the following Amsel criteria: (1) presence of homogeneous greyish-white vaginal discharge; (2) an elevated vaginal pH >4.7; (3) a positive amine odour test on addition of 10% KOH; (4) the presence of clue cells (>2 HPF) on wet mount microscopy. In addition, the BV-blue test (Gryphus Diagnostics LLC) was also performed. This test is a rapid, point of care diagnostic tool for the diagnosis of BV, with a high sensitivity and specificity [9]. The BV-blue is an enzyme activity test for use in detection of sialidase enzyme activity. Vaginal pH was measured using colour strips with a range of 4.0–7.0 (Merck). Vaginal pH was measured 24 h after the last application of MVG or the corresponding placebo. The placebo gel, with an appearance similar to MVG, was made using a polymer (hydroxyethylcellulose) with no buffering activity. Vaginal pH, the BV-blue test and the Whiff test (10% KOH) were performed at baseline and at weeks 6 and 12.

5. Statistical methods

The sample size was based on the assumption of an absolute difference of at least 50%, at the end of 12-weeks study period, in the rate of clinical cure in favour of the vaginal gel in comparison with placebo. With a power of 90% and a type I error of 0.05, a total of at least 40 patients have to be recruited in the trial. Taking into account a potential 10–15% drop-out rate we decided to fix in 45 patients the enrolment goal for this trial. Sample size was calculated using the StudySize (CreoStat HB) ver. 1.07. The Fisher exact test was used to compare categorical variables and the Wilcoxon test and the paired *t*-test were used to compare continuous variables. One-way ANOVA test with Tukey–Kramer comparison test were used to compare repeated measures. P value of <0.05 was considered significant.

6. Results

Between February 2002 and October 2003, 70 outpatients with a vaginal discharge as the major clinical complain, were screened for the study. Fig. 1 shows the trial profile. Forty-five women met the inclusion criteria and were

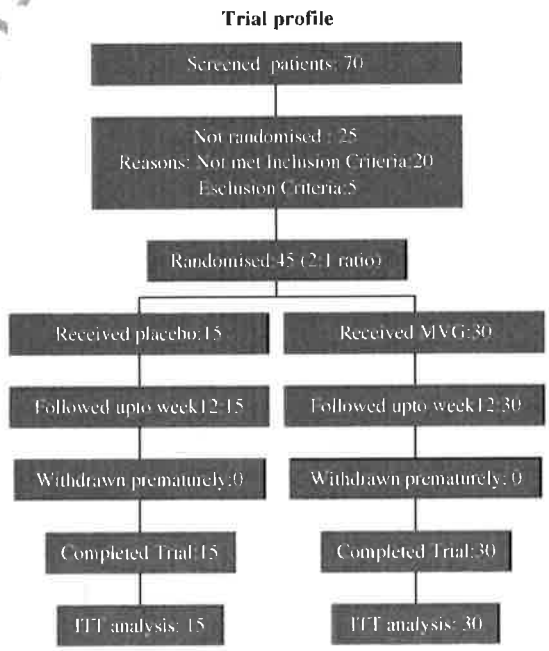

Fig. 1. Study flow-chart.

Table 1
Description of trial population

	Vaginal gel ($n = 30$)	Placebo ($n = 15$)	P value
Age (year) (mean ± S.D.)	42 ± 10	38 ± 9	ns
Race	Caucasian: 100%	Caucasian: 100%	ns
Menopause n (%)	2/30 (8%)	2/15 (16%)	ns
Smoker	6/30 (25%)	2/15 (16%)	ns
History of BV n (%)	20/30 (31%)	8/15 (25%)	ns
Vaginal pH at baseline	6.1 ± .7	5.5 ± .7	ns
BV-blue test positive	30/30 (100%)	15/15 (100%)	ns
Whiff test positive	30/30 (100%)	15/15 (100%)	ns

enrolled in the trial. All patients were valuable for the efficacy and safety analysis on an intention-to-treat basis. Their demographic characteristics are shown in Table 1. At randomisation, BV was confirmed in all subjects. At baseline, the vaginal pH was 6.1 ± 0.7 in the MVG and 5.5 ± 0.7 in the placebo group. At the screening visit, the fish odour and BV-blue tests were positive in all enrolled patient. Clinical cure was defined as absence of vaginal discharge, a vaginal pH <4.6, a negative fish odour test, absence of clue cells at the wet mount microscopy and a Nugent score <7. All enrolled patients concluded the 12-week trial. At the end of the treatment phase (week 6) 28 out of 30 women (93%; 95% CI: from 78 to 98%) in the MVG group were clinically cured in comparison with only 1 out of 15 (6%; 95% CI: from 1.5 to 35%) in the placebo group ($P = 0.0001$, two-side Fisher Exact test). At the end of the follow-up phase (week 12), 86% (26 out of 30) of MVG treated women remained clinically cured in comparison with 8% in the placebo group ($P = 0.0001$). At week 6, the BV-blue test was negative in 28 out of 30 patients (93%) in the MVG group in comparison with 3 out of 15 patients (30%) in the placebo group ($P = 0.002$, two-side Fisher Exact test). In comparison with baseline values, in the MVG group vaginal pH significantly ($P = 0.0001$; ANOVA test for repeated measures) decreased both at the end of treatment phase and at the end of follow-up phase; in contrast, in the placebo group, non-significant modifications of vaginal pH were observed during the trial (Fig. 2). Normalisation of vaginal pH (<4.6) at week 12 was observed in 29 out of 30 women in the MVG group (96%) and in only 1 out of 15 in the placebo group (6%) ($P = 0.001$, two-side Fisher Exact test). The two treatments were well tolerated. A serious adverse event, judged no treatment related, was observed in a MVG patient (endometrial carcinoma).

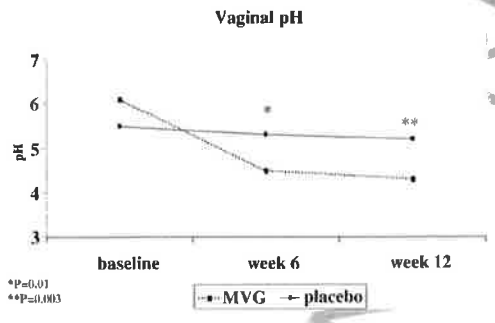

Fig. 2. Vaginal pH in MVG (mucoadhesive vaginal gel) and the placebo group.

7. Discussion

Our results demonstrated for the first time that the use of a non-antimicrobic, non-hormonal bioadhesive vaginal gel with buffering activity is an effective treatment of bacterial vaginosis. In short and medium terms (<12 weeks) this gel induced a clinical cure rate >85%. BV is characterised by the disappearance of lactobacilli and overgrowth of *Gardnerella vaginalis* and anaerobic bacteria [10]. A vaginal pH >4.7 is thought a characteristic sign of this infection [11]. Acidity is considered to be one of the protective mechanisms of the vagina [12]. The mild acidity of the healthy vagina has been shown to correlate with decreased risk for chlamydia, trichomonas and urinary infections. More recently, several studies have shown that an acidic vaginal pH significantly increases the binding capacity of Lactobacilli to the vaginal epithelium [13] and reduces the activity of several pathogenic bacterial enzymes such as sialidase [14]. Adhesion of Gardnerella to vaginal epithelial cells is pH-dependent with a maximum attachment occurring between pH 5 and 6 [15]. The vaginal pH is thus recognised to be the most significant predictor of the status of the vaginal ecosystem [16]. There are several evidences of an association between BV and gynaecologic and obstetric complications [17]. BV has been associated to pelvic inflammatory disease, endometritis and cervicitis [3]. BV responds to oral or topical antibiotic therapy [1]. Nitroimidazole derivatives and clindamycin are used for the treatment of BV [18]. However, a significant percentage of women with BV are not adequately treated. In addition, the recurrence rate of BV remains high despite adequate antibiotic treatment. Reasons for recurrence are unclear but failure to eradicate the offending organisms or to re-establish the normal protective Lactobacillus-dominant vaginal flora are considered the main factors. A persistent high (i.e. >4.7) vaginal pH is a common alteration found in patients with recurrence of BV after effective therapy [7]. In addition to eradicating bacterial strains responsible for BV, a treatment strategy aimed to rapidly normalise vaginal pH could increase the clinical cure rate and reduce recurrent episodes of BV. Previous controlled trials have shown that MVG normalizes vaginal pH in BV patients [8]. Paternoster et al. [19] have recently demonstrated in a randomised, double-blind, placebo controlled study that the use of MVG in pregnant women was able to maintain a physiological vaginal ecosystem and to prevent the increase of vaginal pH and vaginal interleukin-6 levels. In our study, MVG had induced a negativisation of the BV-Blue test in 92% of

treated patients. The BV-blue test evaluates the enzymatic activity of sialidase. This enzyme has an optimal activity at pH of 5.0, whereas its activity decreases by 70% at pH <4.5 [20]. Therefore, a BV-blue negative test could be observed if vaginal pH is in the normal range. The Whiff test is a qualitative assessment of the presence of volatile amines. Volatilisation is a pH-dependent phenomenon. A vaginal pH <4.5 is also an important factor inhibiting pathogen bacterial growth. An higher vaginal pH normalisation rate after therapy in BV patients could be a key element also for normalisation of laboratory diagnostic tests and in reducing recurrences of BV. Our study has demonstrated that a non-antimicrobic, acidic, buffering vaginal gel was superior to placebo in the treatment of BV and in lowering vaginal pH. However, some study limitations have to be taken in account in evaluating our results. We compared the efficacy of MVG with placebo. The primary end point of the study, however, was to evaluate the efficacy of MVG in the treatment of BV, not a comparison with standard care therapy. The clinical cure rate we observed in this trial (93% at week 6 and 86% at week 12) with MVG is comparable with the clinical cure rate with metronidazole or tinidazole [21]. Randomised, prospective, long-term trials with adequate sample size, are warranted to compare the efficacy of MVG in BV treatment with standard therapy care.

8. Condensation

This study demonstrated that the use of a non-antibiotic, non-hormonal, acidic buffering vaginal gel is an effective treatment of bacterial vaginosis.

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