

A new approach for the treatment of bacterial vaginosis: use of polyhexamethylene biguanide. A prospective, randomized study

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Abstract. – *Background:* Bacterial vaginosis (BV) is the most common vulvovaginal infection and represents the 35% of all the infections occurring in women in the reproductive age. It is well recognised that serious forms of BV can induce several complications among women undergoing gynaecologic or obstetric surgery, having pelvic inflammatory diseases, temporary or absolute infertility, miscarriage and abortion. At present, the clinical treatment of choice of BV is the use of systemic or local (gel or cream) metronidazole and clindamycin, though systemic use has some limitations due to side-effects and contraindications. Polyhexamethylene biguanide (PHMB) is a new bi-biguanide compound having a broad spectrum activity and low toxicity, that have been successfully utilized in ophthalmology and dentistry. Aim of this study was to evaluate the efficacy and tolerability of a single-dose vaginal administration of a PHMB vaginal gel in the treatment of BV in comparison to clindamycin vaginal cream.

Methods: One-hundred and ten patients affected by BV were treated with PHMB vaginal gel in single administration or clindamycin vaginal cream 1 daily administration for 7 days.

Results: We demonstrated the therapeutic efficacy of mono-dose administration of a vaginal solution containing PHMB in BV treatment; this efficacy is similar to the one shown in antibiotic therapy. Furthermore, this product was well tolerated by all treated patients.

Conclusions: Mono-dose PHMB treatment should be regarded as the therapy of choice for BV, using clindamycin and metronidazole only for relapses treatment.

Key Words:

Bacterial vaginosis, PHMB, Metronidazole, Clindamycin.

Introduction

Bacterial vaginosis (BV) is the most common vulvovaginal infection and represents the 35%^{1,2} of all the infections occurring in women in the reproductive age. Serious forms of BV can induce complications among women undergoing gynaecologic or obstetric surgery³, having pelvic inflammatory diseases (PID)⁴, temporary or absolute infertility^{5,6}, miscarriage and abortion^{7,8}. Today, after a BV diagnosis, both in presence of a symptomatic or an asymptomatic form (the latter representing the 50% of total cases²), the clinical treatment of choice is the use of systemic or local (gel or cream) metronidazole and clindamycin. However, there are some limitations to the systemic use of these two drugs, due to side-effects that may occur and contraindications, e.g. pregnancy.

Since 1956, Rose and his collaborators demonstrated that biguanide have antimicrobial activity⁹. Chlorhexidine, a bi-biguanide, has been one of the most commonly used biguanides because of its broad spectrum activity and low toxicity¹⁰. Chlorhexidine has a significantly higher bactericidal activity than monomeric biguanides, and this observation has pushed the research towards the study of new bi-biguanide drugs such as polyhexamethylene biguanide (PHMB). Moreover, the clinical use of PHMB in ophthalmology and dentistry has demonstrated that this active component is more tolerated and effective than chlorhexidine^{11,12}. The aim of this study was to evaluate PHMB efficacy in the treatment of BV.

Materials and Methods

The Ethical Committee approval to the study was obtained before the recruitment of patients was started. All patients signed a written informed consent at the enrolment. One-hundred and thirty-three women, aged 18-40 years, suffering for symptoms previously ascribed to BV, were recruited to be screened for inclusion in the trial. The clinical diagnoses were conformed to Amsel criteria¹³ and Scandinavian Society of Vaginal Bacteriosis (SSVB) guidelines¹⁴. Patients meeting at least three of four Amsel criteria and/or both criteria suggested by SSVB were diagnosed as having BV. One hundred and ten of the screened patients resulted affected by BV and were included in the trial. After the inclusion, patients were allocated in two group of treatment according to a randomization table, and a clinical tests and a complete microbiological analysis were performed. Patients were treated according to the following scheme:

Group A (n = 59): 0.10% PHMB gel solution, a single-dose vaginal administration in single application (Monogin® gynaecologic solution, Lo.Li. Pharma, Rome, Italy);

Group B (n = 51): 2% Clindamycin (CL) vaginal cream, one (5 grams) daily application for 7 days.

Patients were re-examined three weeks after treatment cessation. The examiner was blinded to the treatment. In order to perform an objective evaluation of the therapeutic results, the criteria suggested by Dhar¹⁵ and Ahmed-Jushuf¹⁶ were applied. After the completion of the study, the tolerance to the two drugs was estimated taking

into consideration the occurrence of side effects and/or possible alterations of laboratory tests.

Statistical Analysis

A statistical analysis of the data collected during the study was performed. The tests were chosen according to data characteristics. In particular: Friedman and Wilcoxon test were used to evaluate pre- and post-therapy symptoms; The analysis of variance was used to compare data between groups; Kaplan and Meier test for temporal evaluation of relapses [Statistica/W5.1 software (StatSoft-Inc, Tulsa OK-USA)].

Results

The characteristics of the two groups were homogeneous in terms of pre-treatment symptoms and objective anamnesis, enabling the comparison of the results obtained from the two groups after treatment.

Vaginal and vulvar itching and malodorous vaginal discharge were the most common reported symptoms. A total of 24 subjects (21.8%) equally split between the two groups (PHMB group 10/59 vs CL group 14/51; $\chi^2 = 1.7$; $p = ns$) resulted asymptomatic. 89.1% patients reported a typical greyish secretion, 99% reported $pH < 4.5$, 68.1% positive sniff test, 81.8% presence of clue cells, 91.8% reduction or absence of Lactobacilli and predominance of cocci at microscopical observation after Gram staining. The distribution of objective symptoms, required for BV diagnosis, also resulted homogeneously split between the two groups during the pre-treatment evaluation.

Table I. Therapeutic results based on objective diagnostic criteria 3 weeks, 3 months and 6 months after the end of the treatment.

	A Group (PHMB)	B Group (Clindamycin)
Patients (n)	59	51
Evaluable patients (n-%)	53-(89.8)	47-(92.1)
Achievement (n-%)	34-(64.1)	32-(68.1)
Improvement (n-%)	12-(22.6)	9-(19.1)
Failure (n-%)	7-(11.3)	6-(10.6)
Retired from the study (n-%)	6-(10.0)	4-(7.80)
Drug intolerance (n-%)	2-(3.30)	4-(7.80)

One hundred of the total 110 women (90.9%) accomplished the treatment and underwent to the screening planned after three weeks after the end of the treatment. A statistically significant reduction of all symptoms was recorded in the PHMB-treated group. In particular, after PHMB therapy, the frequency of all objective BV symptoms, which are the most reliable signs of therapeutic efficacy, was significantly reduced. In the CL-treated group, a statistically significant reduction of many symptoms, in particular of vaginal and urinary associated symptoms, was recorded. CL therapy showed lower efficacy in terms of resolution of vulvar symptoms, in particular vulvar itching which was still present in 13/19 patients (68.4%). In addition, the reduction of Lactobacilli persisted, after three weeks, in 30/47 (63.8%) CL-treated cases, a significantly higher frequency than that recorded in the PHMB-treated group: 10/53 (18.87%) $\chi^2 = 20.98$; $p < 0.001$.

Global subjective evaluation of the therapy substantially reflects what objectively assessed, with a positive judgement for the two treatments, both in terms of therapeutic efficacy (86% for PHMB-treated group and 85% for CL-treated group) and in terms of compliance (98% and 93.7%, respectively).

Local low or moderate side-effects were reported, but they were so critical to induce to therapy discontinuation. In the CL-treated group, 3 patients (6%) discontinued the therapy, due to the occurrence of intolerance to the drug. At first clinical control after CL therapy, *Candida albicans* superinfections were recorded in 6/47 (12.7%) patients versus only 1 (1.8%) of the 53 PHMB-treated patients.

Discussion

This study demonstrated that pharmaceutical formulations containing PHMB and clindamycin, for topical use in BV treatment, exhibit a similar efficacy. Mono-dose PHMB treatment is a novelty for BV treatment. The benefits ascribed to the treatment were still presents after three weeks from therapy cessation in 86.7% of the treated patients. The treatment also showed low side-effects, limited to local intolerance, and an excellent compliance. Similar results were obtained in the

other group were patients were treated with 2% Clindamycin (CL) vaginal cream, one (5 grams) daily application for 7 days. CL-therapy is today the treatment of choice for BV, with achievements percentage of remittance of the pathology comparable to the one recorded in the present study^{15,17}.

Moreover, Clindamycin was found to have a bactericidal activity also against Lactobacilli, as demonstrated by the persistent reduction of Lactobacilli concentrations observed in the microscopical examinations after Gram staining in the 63.8% of the Clindamycin-treated patients. The consequently reduced self-defence ability of the vaginal ecosystem could be involved in the development of candidosis, occurring in the 12.6% of this group (data in accordance with Livengood et al¹⁷). The occasional occurrence of *Candida* infections in the PHMB-treated group, and the rare susceptibility to this kind of complications in PHMB treated patients could be due to the fungistatic and fungicidal action of PHMB and, above all, to the immediate restarting of lactobacilli growth, observed in the 81.2% of subjects of this group at the first microscopical observation.

Therapeutic efficacy associated to PHMB administration could be attributed to two distinct mechanism:

- 1) a direct antimicrobial action against microbes responsible for BV exerted by PHMB binding to microbic membrane phospholipids (phosphatidilglycerol, phosphatidilethanolamine, etc.)¹⁸. The cellular membranes of the pathogens contain a higher quantity of these phospholipids compared to Lactobacilli membranes, justifying the resistance of Lactobacilli to PHMB¹⁹.
- 2) an indirect action, through a fast restoration of the vaginal ecosystem.

Three weeks after the beginning of the treatment, clue cells disappearance was reported in the 81.2% of the PHMB-treated patients compared to the 78.8% of the CL-treated patients, with a more frequent restoration of Lactobacilli predominance at microscopical observation in the PHMB-treated group. The restarting of lactobacilli growth induces, as foreseen, a significant vaginal pH reduction.

In summary, this study demonstrated the therapeutic efficacy of mono-dose administration of a vaginal solution containing PHMB in BV treatment; this efficacy is similar to the one shown in antibiotic therapy, today used as the elective therapy. Furthermore, this product was well tolerated by all treated patients. Mono-dose PHMB treatment should be regarded as the therapy of choice for BV, using CL and metronidazole only for relapses treatment.

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