

The efficacy and safety of a single dose of Polyhexamethylene Biguanide gynaecologic solution versus a seven-dose regimen of vaginal clindamycin cream in patients with bacterial vaginosis

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Abstract. – Objective: At the present the clinical treatment of choice of bacterial vaginosis (BV) is the use of systemic or local metronidazole or clindamycin. Aim of the study was to evaluate the efficacy and tolerability of a single dose of gynaecologic solution, Polyhexamethylene Biguanide (PHMB), Monogin[®], in the treatment of BV in comparison to a 7-days treatment with clindamycin vaginal cream.

Study Design: This multicenter, randomized, single-blind, parallel-group study enrolled 740 patients with BV infections.

Treatment consisted of either a single intravaginal dose of PHMB or 7 daily doses of Clindamycin. Efficacy and safety were assessed 21-30 days after the start of treatment. The efficacy endpoints were Investigator Cure, Clinical Cure (a composite of all 4 Amsel's criteria and investigator Cure), Nugent Cure (Nugent score < 4), and therapeutic cure (a composite of clinical cure and Nugent Cure). Resolution of individual Amsel's criteria was also evaluated. Any adverse event of the treatment has been monitored throughout the study.

Results: No significant differences has been reported in cure rates between the PHMB and Clindamycin treatment groups in Investigator Cure ($P = 0.702$), Clinical Cure ($P = 0.945$), Nugent Cure ($P = 0.788$), or Therapeutic Cure ($P = 0.572$). Results were also similar for 3 of 4 and 2 of 4 Amsel's criteria and for each individual Amsel's criterion (all P -values > 0.200).

Ninety-five percent confidence intervals for each endpoint were consistent with equivalence between the 2 products. There was no significant difference between the treatment groups in the incidence of treatment-emergent adverse events ($P = 0.386$).

Conclusions: A single dose, of PHMB gynaecologic solution (Monogin[®]) is equivalent in safety and efficacy to a 7-dose regimen of Clindamycin vaginal cream in the treatment of bacterial vaginosis. Furthermore the compliance as been reported to be higher for the single-dose treatment with PHMB than with 7-days treatment with Clindamycin.

Key Words:

Bacterial vaginosis, Vaginitis, Clindamycin vaginal cream, PHMB.

Introduction

Bacterial vaginosis (BV) is currently the most prevalent cause of infectious vaginitis among women attending for genitourinary diseases¹. BV has a complex microbiology. *Lactobacillus* populations, which are usually dominant in healthy women, are replaced by a polymicrobial group of organisms that includes *Gardner vaginalis*, anaerobic Gram-negative rods such as *Prevotella* species, *Peptostreptococcus* species, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and often *Mobiluncus* species. Anaerobic bacteria produce enzymes, aminopeptidases, that degrade protein and decarboxylases that convert amino acids and other compounds to amines. These amines contribute to the signs and symptoms associated with the syndrome, raising the vaginal pH and produc-

ing a discharge odor. The excessive amounts of bacteria characteristic of the syndrome attach to epithelial cell surfaces, resulting in "clue cell". Nearly half the patients report no noticeable symptoms, but many develop a characteristic copious, malodorous discharge if untreated. Results from epidemiologic studies have associated BV with serious upper genital tract infections and adverse pregnancy outcome^{2,3}.

Oral or intravaginal therapy with clindamycin is one of the recommended treatments for BV in nonpregnant women. Both systemic and local administration report similar effectiveness, but local treatment is preferred due to lower side-effects associated with oral antibiotic therapy such as nausea, vomiting, and taste perversion^{4,5}. In addition, patients treated with intravaginal therapies report increased compliance to the treatment compared with those treated with oral therapies⁶. Regarding intravaginal treatment of BV, most of the therapies need a daily treatment for multiple days, that resulting in a low compliance and satisfaction of the patient⁷. Thus, an effective single-dose vaginal treatment for BV might be beneficial to women from a number of different points of view.

Since 1956, Rose et al. demonstrated that biguanide have antimicrobial activity. The most common biguanide widely used is chlorhexidine, because of its broad spectrum activity and low toxicity. Further studies demonstrated that the longer is the chain of the polybiguanide the more bacteriostatic is the product. New polybiguanide drugs have been developed as polyhexamethylene biguanide (PHMB) that resulted in being more effective and tolerated than chlorhexidine. Moreover, the clinical use of PHMB in ophthalmology and dentistry brought more data on the effectiveness and tolerability of the drug in medical fields.

PHMB gynaecologic solution is a single-dose intravaginal therapy for use in the treatment of BV. PHMB is a patented, single-dose, isotonic, topical solution.

Given the ability of PHMB to adhere to vaginal epithelium for a prolonged period of time, we hypothesize that a single dose of PHMB would be equivalent to a 7-day course of a conventional clindamycin phosphate intravaginal cream. Thus, the purpose of the current study was to determine whether a single dose of PHMB is equivalent in safety and efficacy to a 7-day regimen of vaginal cream Clindamycin in the treatment of BV.

Material and methods

The study was designed in accordance with the guidelines for developing effective treatments for BV². This was a multicenter, single (investigator)-blind, active-controlled study. All patients provided signed informed consent before any study-related procedure was performed.

Eligible patients were nonpregnant women at least 18 years of age with a clinical diagnosis of BV, which was defined as meeting all of Amsel's criteria⁹ (> 20% clue cells, off-white [milky or gray], thin, homogeneous vaginal discharge, vaginal pH > 4.5, a fishy amine odor upon the addition of 10% KOH to vaginal fluid ["swiff" test]). Patients were excluded if they were pregnant or nursing; had sexually transmitted infections, had vulvovaginal infections other than BV, had vulvovaginal or cervical abnormalities or disorders; were actively menstruating; had received antifungal or antimicrobial treatment within 14 days of the study; were using intrauterine devices (IUDs); were taking anticoagulants, lithium, disulfiram, or neuromuscular blocking agents; or were hypersensitive to clindamycin, lincomycin, or to any excipient in the drug formulation.

Eligible patients were randomly assigned to 1 of 2 treatment arms PHMB (Monogin[®] – LoLi. Pharma S.r.l., Rome, Italy) or clindamycin cream in a single (investigator)-blind fashion according to a computer-generated randomization schedule. Patients were instructed in the appropriate study medication administration techniques, which were to be performed or started within 48 hours after leaving the clinic.

PHMB consisted of 0.10 PHMB formulated in 100 ml of the vaginal gel solution. Monogin[®] was self-administered by patients in a single dose. Clindamycin vaginal cream consisted of 2% clindamycin phosphate, but formulated in 5 g of a conventional vaginal cream. Clindamycin was self-administered by the patient once daily for 7 consecutive days.

Treatment effectiveness was evaluated and compared at a Test-Of-Cure (TOC) visit 21-30 days following the start of treatment, using several clinical and microbiologic indices. Investigator Cure was based on the Investigator's response (Yes/No) to a question at the TOC visit regarding the need for additional BV treatment. Clinical Cure was a composite endpoint, including resolution of all 4 Amsel's criteria and Investigator Cure. Nugent Cure was defined as a Gram stain

Nugent score¹⁰ < 4 (on a 10-point scale). Therapeutic Cure was a composite endpoint defined as both Clinical Cure and Nugent Cure. In addition, the 4 Amsel's criteria were each evaluated individually. The TOC visit was selected to demonstrate both status and duration of outcome. The per-protocol (PP) population was selected for the efficacy analyses in accordance with demonstration of equivalence between treatments.

The safety of the 2 treatments was evaluated by monitoring treatment-emergent adverse events (AEs) throughout the study.

Statistical Methods

Efficacy endpoints were analyzed using the center-stratified Cochran-Mantel-Haenszel (CMH) estimate of the difference in cure rates and corresponding confidence interval¹¹. PHMB (Monogin[®]) was to be considered equivalent to Clindamycin if the 2-sided 95% confidence interval (CI) for the difference in cure rates (PHMB minus Clindamycin) had a lower limit greater than -20% and an upper limit less than +20%. Efficacy analyses were performed using a PP population, which included patients who administered study medication, had baseline Nugent scores > 4, had assessment results at the TOC visit or discontinued participation in the study prior to the TOC visit due to lack of efficacy, had no antimicrobial therapy for conditions other than BV during the study, started study medication within 48 hours of the entry visit, and had no major violations of the study protocol. All patients who administered at least 1 dose of study medication were included in the safety analyses.

Results

Of the 740 patients enrolled in the study (371 in the PHMB (Monogin[®]) group and 369 in the Clindamycin group, 347 (46.9%) were considered evaluable for the PP population (175 in the PHMB group and 172 in the Clindamycin group). Of the 393 patients who were not evaluable in the PP population, 126 had baseline Nugent scores < 4, 88 participated in the study for less than 21 days but were not treatment failures, and 71 did not start study medication within 48 hours of the Entry Visit. These 3 reasons account for approximately 75% of the patients who were not evaluable in the PP population. The percentages of patients with each primary reason for

non-evaluability were similar between the treatment groups. A complete listing of the primary reasons for non-evaluability in the PP population by treatment group is in Table I.

Cure of BV was evaluated by a number of different measures. Frequencies of Investigator Cure, Clinical Cure, Nugent Cure, and Therapeutic Cure are presented in Table II.

The Investigator Cure represents the investigator's assessment of the need for additional therapy for BV at the TOC Visit. Investigator Cure (no additional therapy required for BV) was achieved in 89.1% of PHMB patients and 86.4% of Clindamycin patients at the TOC visit. There were no statistically significant differences in Investigator Cure rates between treatment groups ($P=0.702$) and the 95% CIs for the differences were consistent with equivalence with regard to the need for additional treatment of BV as assessed by the Investigator.

Clinical Cure, which represents both alleviation of BV signs and symptoms and alleviation of the need for additional BV therapy at the TOC visit, was achieved in 64.3% of PHMB patients and 63.2% of Clindamycin patients. There were no statistically significant differences in Clinical Cure rates between treatment groups ($P = 0.945$).

Similar cure rates were also observed in the 2 treatment groups when less stringent criteria were used to define cure. If 3 of the 4 Amsel's criteria are used to define cure, 87.5% of PHMB patients and 83.2% of Clindamycin patients are cured ($P = 0.399$). When 2 of the 4 Amsel's criteria are used to define cure, cure rates increase to 90.6% of PHMB patients and 91.2% of Clindamycin patients ($P = 0.792$). There were no statistically significant differences in cure rates between treatment groups and the 95% CIs for each differences were consistent with equivalence in the alleviation of BV signs using both 2 and 3 of the 4 Amsel's criteria. In addition, there were no statistically significant differences in resolution of Amsel's criteria between the treatment groups when the criteria for clue cells (< 20%) and a negative "whiff" test were evaluated together ($P = 0.965$) or when the criteria for clue cells, "whiff" test, and vaginal pH (< 4.7) were evaluated together ($P = 0.539$). The cure rates associated with each Amsel's criterion and selected groups of criteria are presented in Table III.

Spiegel et al.⁹ defined a scoring system to measure microbiologically BV, based on some of the bacterial cell types that can be seen in Gram

Table I. Primary reasons for non-evaluability in the per-protocol population by treatment group.

Reason	Monogin® (N = 371) [‡]		Clindamycin (N = 369) [‡]		Overall [†] (N = 740) [‡]	
	n [§]	(%) [§]	n [§]	(%) [§]	n [§]	(%) [§]
Did not take study medication	11	(3.0)	6	(1.5)	17	(2.2)
Did not take Clindamycin on consecutive days	3	–	25	(6.7)	25	(3.3)
Baseline Nugent score < 4	57	(15.5)	69	(18.6)	126	(17.0)
Did not take study medication with 48 hours of the entry visit	46	(12.5)	25	(6.7)	71	(9.6)
Participated in the study for < 21 days without treatment failure	51	(13.7)	37	(10.0)	88	(11.9)
Received antimicrobial therapy for reasons other than bacterial vaginosis	10	(2.6)	19	(5.2)	29	(3.9)
Used other intravaginal products or had intercourse within 7 days of start of treatment	15	(4.1)	12	(3.3)	27	(3.7)
Did not meet all inclusion and exclusion criteria	4	(1.1)	4	(1.1)	8	(1.1)
Participated in the study for > 40 days	1	(0.4)	1	(0.4)	2	(0.4)
Total patients not evaluable	196	(52.8)	197	(53.5)	393	(53.1)
Total patients evaluable	175	(47.2)	172	(46.5)	347	(46.9)

^{††}Overall refers to the total number of patients enrolled; [‡]Denotes total number of patients enrolled by and across treatment group; [§]n and % denote the number and percentage of evaluable and nonevaluable patients by reason for each treatment group.

stained smears of vaginal secretion. This was later refined by Nugent et al.¹⁰, who provided a scoring system that evaluates the changes in vaginal microflora, from the normal condition to bacterial vaginosis status, as a continuum.

Nugent Cure (Nugent score ≤ 4) was achieved in 56.5% of PHMB patients and 57.7% of Clindamycin patients at the TOC visit. There were no statistically significant differences in Nugent Cure rates between treatment groups ($P \sim 0.788$) and the 95% CIs for the differences were consistent with equivalence in Nugent Cure rates at the TOC Visit.

Therapeutic Cure represents the composite of Clinical Cure and Nugent Cure at the TOC visit. Analysis results demonstrate that 72 (42.1%) patients in the PHMB group achieved Therapeutic Cure compared with 78 (45.6%) patients in the Clindamycin group. Therapeutic Cure results indicate that a single dose of PHMB is statistically equivalent in effectiveness to 7 daily doses of Clindamycin in the treatment of BV ($P = 0.572$).

Among the 355 patients in the PHMB group and the 361 patients in the Clindamycin group that received at least I dose of study medication, 108 Monogin®-treated patients (30.4%) and 97

Table II. Efficacy outcomes at: the Test-of-Cure Visit (number and % of evaluable patients cured).

Endpoint	Monogin®			Clindamycin			Treatment differences [§]		
	N [†]	n	(%) [‡]	N [†]	n	(%) [‡]	%	95% CI	P-value
Investigator Cure	175	156	(89.1)	172	149	(86.4)	2.7	[-5.4, 10.7]	0.702
Clinical Cure1	170	109	(64.3)	172	109	(63.2)	1.1	[-10.8, 13.0]	0.945
Nugent score < 4	169	95	(56.5)	169	98	(57.7)	-1.3	[-13.6, 11.1]	0.788
Therapeutic Cure1	170	72	(42.1)	172	78	(45.6)	-3.5	[-15.8, 8.7]	0.572

^{††}Overall refers to the total number of patients enrolled; [‡]Denotes total number of patients enrolled by and across treatment group; [§]n and % denote the number and percentage of evaluable and nonevaluable patients by reason for each treatment group.

Table III. Number and percent of patients with resolution of individual Amsel's criteria at the Test-of-Cure Visit.

Endpoint	Monogin®			Clindamycin			Treatment differences [§]		
	N [†]	n	(%) [‡]	N [†]	n	(%) [‡]	%	95% CI	P-value
3 of 4 Amsel's criteria resolved	175	153	(87.5)	170	141	(83.2)	4.3	[-4.4, 13.0]	0.399
2 of 4 Amsel's criteria resolved	175	159	(90.6)	170	155	(91.2)	-0.6	[-7.7, 6.5]	0.792
< 20% Clue cells	175	153	(87.5)	170	143	(84.0)	3.5	[-5.1, 12.1]	0.480
Negative "whiff" test	175	159	(90.6)	170	160	(94.4)	-3.8	[-10.2, 2.7]	0.205
Normal discharge	175	148	(84.4)	170	147	(86.4)	-2.0	[-10.7, 6.7]	0.545
pH < 4.7	173	128	(74.0)	165	118	(71.3)	2.7	[-8.4, 13.8]	0.668
Clue cells + "whiff" test	175	148	(84.4)	170	143	(84.0)	0.4	[-8.6, 9.4]	0.965
Clue cells 4- "whiff" test + pH	173	119	(68.5)	165	107	(64.8)	3.7	[-8.0, 15.5]	0.539

[†]"Overall" refers to the total number of patients enrolled; [‡]Denotes total number of patients enrolled by and across treatment group; [§]n and % denote the number and percentage of evaluable and non-evaluable patients by reason for each treatment group.

Clindamycin-treated patients (26.8%) had a total of 115 and 97 treatment-emergent AEs, respectively, during the study. The most commonly reported AEs are shown in Table IV. Thirty-seven patients (10.3%) in the PHMB group reported 29 study medication-related AEs compared with 29 patients (7.9%) in the Clindamycin group who reported 22 study medication-related AEs. The number of patients who reported AEs and study medication-related AEs were not statistically different between the 2 treatment groups ($P = 0.386$ for overall AEs and $P = 0.336$ for study medica-

tion-related AEs). Overall, among the 716 patients who received study medication, 6 (0.9%) were discontinued from the study due to AEs. Four (1.1%) PHMB-treated patients were discontinued due to Vaginal Yeast Infection, Candidiasis, and Allergic Reaction, to Study Drug. Three patients (0.8%) in the Clindamycin group were discontinued due to Vaginal Yeast Infections. There was 1 serious AE (cellulitis) reported by a patient receiving Clindamycin during the study. The event was judged to be unrelated to the study medication by the investigator.

Table IV. Most commonly reported adverse events (intent-to-treat population).

Endpoint	Monogin® (N = 355) [§]		Clindamycin (N = 361) [§]		Treatment difference [‡]	
	n	(%) [§]	n	(%) [§]	95% CI	P-value [†]
Infections and infestations	3	(0.8)	4	(1.1)	[-2.0, 1.3]	1.000
Urinary tract infection	51	(14.4)	37	(10.2)	[1.3, 9.9]	0.146
Vaginosis, fungal						
Nervous system disorders	5	(1.5)	5	(1.5)	[-2.1, 2.1]	1.000
Headache						
Pregnancy, puerperium, and perinatal conditions	4	(1.1)	1	(0.4)	[-0.7, 2.2]	0.371
Pregnancy						
Reproductive system and breast disorders						
Vaginal discharge	3	(0.8)	4	(1.1)	[2.0, 1.3]	1.000
Vaginal hemorrhage	0	(0.0)	4	(1.1)	[2.4, 0.1]	0.248
Vulvovaginal pruritus	15	(4.2)	11	(3.0)	[-2.0, 4.3]	0.494

[†]Reported by > 1% of patients in any treatment group; [‡]Monogin® minus Clindamycin cure rates; [§]N Denotes the number of patients with non-missing data in the PP population for each treatment group, n and % denote the frequency of patients cured in the PP population within each endpoint; for each treatment group[†] P-value was derived using FET to determine if rates of events differed between treatment groups.

Discussion

As we hypothesized, and confirmed in the results of our previous pilot study¹², analyses of interpretive, symptomatic, and diagnostic efficacy variables revealed no statistically significant differences between use of PHMB (Monogin®) chloride, administered in a single-dose gynecologic solution, and in a standard 7-day vaginal cream (Clindamycin).

Investigator cure is an interpretive measure representing the requirement for additional therapy for BV in the medical opinion of the clinical investigator. Clinical Cure is a conservative symptomatic measure representing resolution of all 4 of the Amsel's criteria as well as a favorable assessment of cure by the investigator. The Nugent score represents a diagnostic evaluation of BV that is not often used in clinical practice. Therapeutic Cure, which requires both clinical cure and Nugent Cure, represents a very conservative composite outcome combining symptomatic, interpretive, and diagnostic measures of BV that has not previously been used as an endpoint. The definitions of Clinical Cure and Therapeutic Cure used here are considerably more conservative than definitions used in previous studies. Although these more conservative criteria for cure are compliant with the 1998 CDER guidance for the evaluation of BV in clinical studies, they may result in lower cure rates than reported in previous studies.

Resolution of 3 of the 4 Amsel's criteria may be more representative of the evaluation of BV in clinical practice. Cure rates using this endpoint were comparable between the PHMB and Clindamycin groups. A study evaluating a 7-day dosing regimen with Clindamycin and a 7-day, twice-daily dosing regimen with 0.75% metronidazole vaginal gel defined BV cure as resolution in this manner and reported 86.2% and 75.0% cure rates for Clindamycin and 0.75% metronidazole, respectively⁵. Although there may be some differences between these studies (e.g., study populations, inclusion criteria, patient evaluability), the cure rates observed were comparable to the 87.5% and 83.2% rates observed using the same definition of cure with PHMB and Clindamycin, respectively, in this study. Previous clinical studies performed with Clindamycin defined BV cure as resolution of 2 of Amsel's criteria (the "whiff" test and clue cell criteria) and reported a cure rate of 86% for a 7-

day dosing regimen. This is comparable to the 84.4% and 84.0% cure rates observed using these 2 criteria with PHMB and Clindamycin, respectively, in this study.

In the study reported here, there were no significant differences in the incidence of AEs between the treatment groups, and AEs commonly associated with oral therapy (e.g., nausea, taste perversion) were reported in less than 1% of the patients in either treatment group.

Conclusions

Overall, a single-dose regimen of PHMB (Monogin®) was shown to be comparable with respect to both efficacy and safety to Clindamycin (Cleocin®). PHMB, however, provides equivalent efficacy and safety in a single dose, compared with a 7-dose regimen of Clindamycin. It has been shown that reducing dose frequency increases the patient's compliance with treatment, symptom control, satisfaction with treatment, and quality of life in a number of disease states⁷. PHMB offers these advantages, and therefore represents an important therapeutic advance in the treatment of BV.

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