The treatment of bacterial vaginosis with a 3 day course of 2% clindamycin cream: results of a multicentre, double blind, placebo controlled trial

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Abstract

Objective—To evaluate the efficacy and safety of a 3 day course of intravaginal clindamycin 2% cream for the treatment of bacterial vaginosis.

Design—A prospective, randomised, double-blind placebo controlled study.

Setting—Departments of genitourinary medicine at Birmingham, Nottingham, Liverpool, Swansea, Leeds, Walsall, Stoke Mandeville, Southampton, Plymouth, Bishop's Stortford and Glasgow.

Subjects—Pre-menopausal women aged 18 years and over, who had symptomatic bacterial vaginosis were randomly allocated to receive either clindamycin 2% cream 5 grams (107 patients) or matching placebo cream (114 patients), daily for three days. Response to therapy was assessed at 7 days (Visit 2) and 28 days (Visit 3).

Results—221 patients with symptomatic bacterial vaginosis were enrolled to the study and of these 141 (63.8%) completed the study. On the "intent-to-treat" (ITT) analysis, 75% of the clindamycin group were classified as "success" or "improved" at visit 2 compared with 13% of the placebo group ($p < 0.001$). At Visit 3, 41% of the clindamycin group were classified as either "success" or "improved" versus 4% in the placebo group ($p < 0.001$). Of the 80 patients who were recorded "success" or "improved" at visit 2, 20 (25%) were reported to have a "recurrence" of BV at Visit 3. The meta-analysis on those who were evaluable at Visit 2 and 3 also showed that clindamycin cream 2% was an effective treatment for bacterial vaginosis, and the differences between the clindamycin group and the placebo group were statistically significant.

Conclusion—We conclude that a 3 day course of clindamycin 2% cream is an effective, and well tolerated treatment for bacterial vaginosis.

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Introduction

Bacterial vaginosis (BV) is considered to be the commonest condition associated with vaginal discharge seen in genitourinary medi-

cine clinics in England.¹ It is characterised by a fishy-smelling vaginal discharge associated with increased vaginal pH.² Microscopic examination of a Gram-stained or wet mounted specimen of vaginal secretions shows a characteristic mixed bacterial flora associated with the presence of clue cells (vaginal epithelial cells covered with polymorphic bacteria). Whilst the exact aetiology of this condition remains unknown, BV occurs when the vaginal ecology is altered and the lactobacilli in normal vaginal fluid are replaced by a mixed bacterial flora predominantly consisting of *Gardnerella vaginalis*, *Mobiluncus* spp., other anaerobes and *Mycoplasma hominis*.

Oral metronidazole has been the treatment of choice since Pheifer *et al* first reported its efficacy in 1978.³ However, relapse rates are high^{4,5} and unpleasant side effects and concern about the use of metronidazole in pregnancy have limited its use in some patients.

Clindamycin has proved to be an effective treatment for BV when given orally.⁶ Good results have also been shown using 2% clindamycin vaginal cream applied twice daily for five days⁷ or once daily for seven days.⁸ More recently, a pilot study showed a three day course of 2% clindamycin vaginal cream to be efficacious⁹ with an 80% cure/improved rate. We conducted this prospective, randomised, double-blind, placebo-controlled study to seek to confirm the results of the pilot study in a multi-centre environment.

Patients and methods

Patients were recruited to the study from departments of genitourinary medicine at the participating centres at Birmingham, Nottingham, Liverpool, Swansea, Leeds, Walsall, Stoke Mandeville, Southampton, Plymouth, Bishop's Stortford and Glasgow. Protocol approval was obtained from the local ethics committees at each site and written informed consent was obtained from each patient.

Pre-menopausal women aged over 18 years who either spontaneously or on direct questioning had symptoms suggestive of BV were included. The diagnosis of BV was based on the following criteria: the presence of an increased, thin homogeneous, malodorous vaginal discharge, vaginal pH > 4.5 using a narrow range (pH 4-6) pH paper, a fishy amine odour after adding 10% potassium hydroxide (KOH) to the vaginal secretion (amine test), the presence of clue cells in the

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vaginal fluid found on microscopic examination, and a Gram stain consistent with the diagnosis of BV (a marked decrease or absence of lactobacilli morphotypes and a marked increase in other Gram variable morphotypes).

Women were excluded if they were menstruating at the initial visit or their period was due within seven days. Other exclusion criteria were: known allergy to clindamycin, pregnancy or breast feeding, the presence of an intrauterine contraceptive device (IUD), women not taking adequate contraception, a history of antibiotic associated colitis, inflammatory bowel disease or diarrhoea, atrophic vaginitis, clinical evidence of genital herpes, warts on the cervix or vaginal vault, symptoms suggestive of pelvic inflammatory disease (PID), a history of systemic or vaginal antimicrobial therapy within the previous two weeks, a baseline diagnosis of chlamydial, gonococcal, trichomonal or candidal infection or any other serious or uncontrolled disease. Women who had participated in other clinical trials within the past three months and those who had had a hysterectomy were also excluded. Clinical evaluation at each visit included a medical and sexual history, genital examination and assessment of vaginal discharge. Vaginal pH was assessed and an amine test was performed. A wet mounted preparation of vaginal secretions was examined for the presence of clue cells, *Trichomonas vaginalis* and *Candida spp.* A Gram-stained smear of vaginal secretions was also examined. Tests for gonorrhoea and chlamydia were carried out as was routine at each clinic.

Patients were randomly allocated to receive 20 g of 2% clindamycin vaginal cream or 20 g matching placebo cream with three disposable applicators designed to deliver 5 g of cream. They were instructed to insert one applicator full of cream high into the vagina for three consecutive nights and to return any unused cream at the next clinic attendance. Follow-up appointments were made at seven days (visit 2) and 28 days (visit 3) after treatment. They were also asked to refrain from sexual intercourse and prolonged bathing until their first follow-up visit.

The criteria for treatment success, "improved", or failure (at visit 2 and 3) are summarised in table 1.

Statistical analysis for comparison of success, improvement, treatment failure or recurrence between the two groups was done by Chi square methods, whilst comparability of the two groups with respect to age, ethnicity, previous medical or gynaecological history, genital infections including gonorrhoea, chlamydia, pelvic inflammatory disease (PID), syphilis, trichomoniasis, candidiasis, or the presence of other specific genital infection at baseline, and previous episode of BV were done using analysis of variance. All data processing and summarisation were conducted using the Statistical Analysis System (SAS) Version 6.08 software package. The data were analysed on an "intent to treat" basis, and further meta analysis was carried

out on the basis of those patients who were evaluable at Visits 2 and 3. Patients were considered evaluable at Visit 2 if they had met the baseline criteria, did not have any other genital infections such as trichomoniasis, gonorrhoea, chlamydia or candida, did not menstruate during treatment, abstained from intercourse, completed the study medication, and attended within the period of 6–17 days. Those who then attended for Visit 3 and had met the Visit 2 evaluability criteria, did not receive antibiotics, and attended within 17–42 days after being prescribed the trial medication were considered evaluable at visit 3.

Results

Two hundred and twenty one women (107 in treatment group and 114 placebo group) were enrolled, and of these 141 (63.8%) completed the study.

Comparison between the two groups for age, ethnicity, previous medical or gynaecological history, genital infections including gonorrhoea, chlamydia, PID, syphilis, trichomoniasis, candidiasis, or the presence of other specific genital infection at baseline, and previous episode of BV showed no significant differences. All patients who attended at least one of the post treatment visits—either Visit 2 (195 patients) or Visit 3 (148 patients)—were included in the intent-to-treat analysis. The numbers of patients in each group attending visits 2 and 3 are summarised in table 2.

On the intent-to-treat analysis, 75% of the clindamycin group were classified as "success" or "improved" at visit 2 compared with 13% of the placebo group ($p < 0.001$). At Visit 3, 41% of the clindamycin group were classified as either "success" or "improved" versus 4% in the placebo group ($p < 0.001$). Of the 80 patients who were recorded "success" or "improved" at Visit 2, 20 (25%) were reported to have a "recurrence" of BV at Visit 3. These results are summarised in table 3.

The outcomes of patients evaluable at Visits 2 and 3 are summarised in table 4. The differences between the clindamycin group and the placebo group was significant ($p < 0.001$).

Thirty eight patients from the clindamycin group and 48 from the placebo group were considered to be non-evaluable at Visit 2. The reasons for this are summarised in table 5.

Clindamycin 2% cream was well tolerated in the study; the frequency of vaginal irritation, vulval soreness, candida vaginitis and

Table 1 Criteria for outcome of treatment

Success: BV not present based on:
1. Absence of symptoms
2. Gram-stain negative
3. Absence of clue cells
4. Normal vaginal fluid
5. Vaginal fluid pH ≤ 4.5
6. Negative amine test
Improved
Criteria 1–3 as above BUT two or less of 4–6 above.
Failure
BV not resolved based on:
1. Symptoms attributable to BV and/or
2. Gram-stain positive and/or
3. Presence of clue cells
Recurrence (visit 3)
Following either success or "improved" at visit 2, BV present as per criteria described in method.

Table 2 Number of patients in each treatment group completing various study periods, intent-to-treat

	2% Clindamycin	Placebo	Total
Randomised	107	114	221
Visit 2—Attended	96	99	195
—DNA	11	15	
—Evaluable	69	66	
Visit 3—Attended*	69	30	99
—DNA	30	43	
—Evaluable	52	18	
Prescribed alternative antibiotic at Visit 2	8	41	49

*Excludes patients prescribed alternative antibiotic therapy

Table 3 Analysis of primary efficacy variables, intent-to-treat

	2% Clindamycin (n = 107)		Placebo (n = 114)	
	Visit 2	Visit 3	Visit 2	Visit 3
Success n (%)	49 (45.8)	42 (39.3)	13 (11.4)	5 (4.4)
Improved n (%)	31 (29.0)	2 (1.9)	2 (1.8)	0
Failure n (%)	13 (12.1)	11 (10.3)*	81 (71.1)	61 (53.5)*
ME-Failure† n (%)	1 (0.9)	N/A	1 (0.9)	N/A
Recurrence n (%)	N/A	20 (18.7)	N/A	5 (4.4)
Missing/DNA n (%)	13 (12.1)	32 (29.9)	17 (14.9)	43 (37.7)

*Includes patients (8 clindamycin, 41 placebo) who received alternative antibiotics.
†ME-Failure = Medical Event Failure.

Table 4 Analysis of primary efficacy variables, evaluable patients

	2% Clindamycin (n = 69)		Placebo (n = 66)	
	Visit 2	Visit 3	Visit 2	Visit 3
Success n (%)	38 (55.1)	33 (63.5)	6 (9.1)	4 (22.2)
Improved n (%)	21 (30.4)	1 (1.9)	1 (1.5)	0
Failure n (%)	10 (14.5)	3 (5.8)	58 (87.9)	11 (61.1)
ME-Failure n (%)*	0	N/A	1 (1.5)	N/A
Recurrence n (%)	N/A	15 (28.8)	N/A	3 (16.7)

ME-Failure = medical event failure.

Table 5 Evaluability status at Visit 2

	Clindamycin	Placebo
Evaluable at Visit 2	69	66
Non-evaluable at Visit 2		
Chlamydia	3	6
Gonorrhoea	1	1
Candida	7	15
Protocol violation	27	26

P > 0.5.

PID was similar in the treatment and placebo groups. *Candida albicans* was detected in eight subjects in each group. Vulvo-vaginal irritation and/or soreness was reported by 11 patients in the treatment group compared with two in the placebo group. Diarrhoea was reported by five patients in the treatment group compared with one from the placebo group, whilst abdominal pain was similarly reported from both groups (three from the treatment group, four from the placebo group). In all the cases, these symptoms were mild and resolved spontaneously without requiring any treatment or investigations. The differences between the groups were not significant.

Discussion

This study shows that a 3-day course of 2% intravaginal clindamycin cream is an effective treatment for BV. On the basis of intent-to-treat analysis, 75% of the treatment group were classed as “success” or “improved” at Visit 2 as compared with 13% of the placebo group. At Visit 3, 41% of the clindamycin group were classified as either “success” or “improved” versus 4% in the placebo group. These differences were highly significant (p < 0.001). Similar data were obtained on the meta-analysis on those who were evaluable at Visit 2 and 3. Our results are comparable with

the reported success rates of seven days treatment with the cream or oral metronidazole.⁸ The findings are also comparable to the earlier pilot study⁹ using a 3-day course of intravaginal clindamycin 2% cream for the treatment of BV. Recurrence of BV was found in 25% (20/80) of those in the treatment group who were assessed as “success” or “improved” at Visit 2. This is comparable to the recurrence rates (0–22%) shown in other studies using clindamycin cream 2% for seven days in BV.^{10,11} The recurrence rates at four weeks (visit 3) shown in this study are also comparable with those using oral metronidazole for seven days where recurrence rates of 10–30% have been reported.^{4,5}

Clindamycin 2% cream was well tolerated in this study with reports of medical events being similar in the two groups. *Candida albicans* was isolated from eight patients in each group. However, vulval irritation/soreness was reported by 11 patients in the treatment group compared with two in the placebo group. The severity of symptoms was mild and the differences were not statistically significant. Diarrhoea was also more commonly reported in the treatment group (five versus one from the placebo group). This difference was not significant and the symptoms were reported as mild.

Conclusions

We conclude that 5 g clindamycin 2% cream used intravaginally for three days is a well tolerated and effective treatment for BV.

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