Original article

Treatment of male partners and recurrence of bacterial vaginosis: a randomised trial

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Objective: To test the efficacy of treatment with clindamycin of a partner on the recurrence rate of bacterial vaginosis in women within 3 months from diagnosis.
Subjects: Eligible for the study were sexually active women with one current sexual partner, who were aged 18–45 years, with a clinical diagnosis of bacterial vaginosis and whose partner agreed to be treated.
Methods: A double blind, randomised, controlled trial was conducted comparing the effect of treating the partner with either clindamycin capsules or placebo on the reduction of the recurrence rate of bacterial vaginosis. Women were treated with clindamycin 2% vaginal cream, administered intravaginally once daily at bedtime for 7 consecutive days. The partners were randomly allocated to clindamycin hydrochloride capsules, 150 g by mouth four times daily for 7 consecutive days, or a placebo. A total of 139 couples were randomised—69 were treated with clindamycin vaginal cream group and 70 with placebo. One, 4, and 12 weeks after the end of treatment the patients and their partners were examined; vaginal discharges were examined to check for clue cells, vaginal pH was determined, and a KOH test carried out.
Results: Overall, 131 women out of the 139 who entered the study were cured (94·2%, lower 95% confidence interval 79·8, based on Poisson's approximation). There was no difference in the cure rate among women whose partner received clindamycin or placebo (χ^2_1 p = not significant). A total of 55 couples (26 in the clindamycin and 29 in the placebo group) withdrew from the study during the follow up period. Of the 69 women whose partner received clindamycin, 22 (31·9%) reported "recurrence" or persistence. The corresponding number was 21 (30%) of the 70 women whose partner received placebo (χ^2_1 p = not significant). Of the 84 couples in which the woman was cured by the first week's visit and who completed the study; there were five recurrences (11·6%) among the 43 women whose partner received clindamycin and nine (22·0%) of the 41 whose partner received placebo (χ^2_1 p = not significant).
Conclusion: This study indicates that vaginal clindamycin is effective and safe in the treatment of bacterial vaginosis, but it does not support the suggestion that male treatment markedly reduces the short term recurrence rate.
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Keywords: bacterial vaginosis; partner; clindamycin

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Introduction

Some clinical observations have suggested that bacterial vaginosis is a sexually transmitted disease.[1–4] It has also been suggested that, in cases of symptomatic bacterial vaginosis, treatment of the sexual partner may reduce the risk of recurrence, which ranges from about 5% to 20%.[5–7] However, the data on the efficacy of treating the partner are scanty and controversial.[8–12] In three studies no relation emerged between oral therapy of the partner and recurrence rate.[8–10] A recent well designed trial with a large sample size showed the utility of treating the male[11] in reducing the recurrence of bacterial vaginosis. In these trials, the partner was treated with oral metronidazole, at different dosages,[8–11] or tinidazole.[9]

In controlled trials, oral clindamycin has been shown to be as effective as oral metronidazole, or more so, in the treatment of bacterial vaginosis.[13] Systemic metronidazole causes nausea, a bitter taste in the mouth, rarely, peripheral neuropathy, and interacts with alcohol ingestion. In addition, metronidazole may cause malformations during pregnancy, so its use must be discouraged in fertile women.[14]

We tested the efficacy of treatment with clindamycin of the partner on the recurrence rate within 3 months from diagnosis and treatment of bacterial vaginosis.

Patients and methods

This was a double blind, randomised, controlled trial comparing the treatment of the partner with either clindamycin capsules or placebo in the reduction of the recurrence rate of bacterial vaginosis after women had been treated with clindamycin vaginal cream for 7 days.

Eligible for the study were sexually active women with one current sexual partner, aged 18–45 years, with a clinical diagnosis of bacterial vaginosis and whose partner agreed to be treated. The study was conducted in 14 outpatient clinics during the period January and December 1994.

Bacterial vaginosis was defined as the presence of clue cells on a wet mount slide plus at least two of the following: vaginal discharge

with pH > 4·5; an increased thin homogeneous vaginal discharge that adheres to vaginal walls; and release of amine odour from a sample of the discharge after addition of 10% KOH.[15]

Patients treated with systemic or topical antibacterial agents in the 2 weeks before diagnosis of bacterial vaginosis, using an intrauterine device or whose partner used a condom, or with clinical evidence of current mucopurulent cervicitis, candidiasis, *Trichomonas vaginalis*, herpes genitalis, papillomavirus, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae* infection were not included.

Women were treated with clindamycin 2% vaginal cream, administered intravaginally once daily at bedtime for 7 consecutive days. The partners were randomly allocated to clindamycin hydrochloride capsules, 150 mg by mouth four times daily for 7 consecutive days, or placebo. Patients were invited to abstain from intercourse during the treatment period and for 1 week after the end of treatment.

A total of 139 couples were randomised—69 in the clindamycin vaginal cream group and 70 in the placebo group.

One, 4, and 12 weeks after the start of treatment the patients and their partners had a clinical examination, including the collection of slides of vaginal discharge to check for clue cells, the determination of vaginal pH, and a KOH test. At both visits, the patient and her partner were asked about side effects and medical events.

Cure was defined as the absence of clue cells plus at least two of the following: vaginal pH < 4·5; negative 10% KOH sniff test; grossly normal vaginal discharge (defined as translucent white, flocculent, low volume). Recurrence was defined as the presence of clue cells on the wet mount slide plus at least two of the following: vaginal discharge with pH > 4·5; an increased thin homogeneous vaginal discharge that adheres to vaginal walls; and release of amine odour from a sample of the discharge after addition of 10% KOH.

Patients not cured 1 week after treatment, who relapsed, or who stopped attending the follow up visits, were classified as "non-responders" in the analysis. The research protocol was approved independently by the ethics committees of individual centres, which established the procedures for obtaining informed consent. Before a couple entered the study, informed consent was obtained from both partners.

STATISTICAL ANALYSIS

The end point of the study was to compare the recurrence rate 12 weeks after bacterial vaginosis in women whose sexual partner was treated with oral clindamycin or placebo. We planned to include about 150 patients. This sample size would give a high probability (β = 0·80) of detection, at a reasonable level of statistical significance (α = 0·05) of a decreased probability of recurrence, from 30% in women whose partner was treated with placebo to 10% in women whose partner was treated with clindamycin.

For the intention to treat evaluation, any patient not cured after vaginal treatment with clindamycin, with medical events or lost during the treatment period, was considered a "non-responder". In the efficacy analysis we considered only women cured at the first week's visit, who completed the study according to the protocol. The difference in the frequency of recurrences between the two groups was analysed using the χ^2 test.

Table 1 Characteristics of patients according to treatment—Italy, 1994–5

	Clindamycin No (%, range)*	*Placebo No (%, range)*
Female age (years)	31·7 (6·5, 20–45)	33·3 (6·2, 21–45)
Female weight (kg)	57·8 (8·2, 38·0–82·0)	57·5 (7·7, 44·5–80·0)
Marital status:		
Not married	23 (33·3)	17 (24·3)
Married	46 (66·7)	53 (75·7)
Incidence sexual intercourse during the 3 months before study entry:		
⩽ 15	35 (52·2)	33 (48·5)
> 15	32 (47·8)	35 (51·5)
Interval from last sexual intercourse (days)	5·1 (35, 1–15)	6·0 (5·7, 0–30)
Contraceptive habits:		
None	46 (66·7)	44 (63·8)
Oral contraceptive	18 (26·1)	22 (31·9)
Barrier methods	5 (7·2)	3 (4·3)
History of pelvic/vaginal infection:		
No	53 (79·1)	47 (68·1)
Yes	14 (20·9)	22 (31·9)
Male age (years)	35·5 (7·4, 22–56)	37·1 (6·9, 22–53)
History of male urethritis:		
No	67 (98·5)	65 (95·6)
Yes	1 (1·5)	3 (4·4)
Incidence sexual intercourse during follow up period:		
2–5 weeks	7·6 (3·6)	7·7 (5·8)
6–9 weeks	9·7 (4·9)	10·4 (7·7)
10–13 weeks	10·3 (5·6)	11·7 (7·6)

*In some cases the sum does not add up to the total because of missing values.

Table 2 Cure rate of bacterial vaginosis after female treatment 1 week after start of treatment—Italy, 1994–5*

	Total series No (%)	*Partner's treatment*	
		Clindamycin No (%)	*Placebo No (%)*
Cured	131 (94·9)	66 (95·7)	65 (94·2)
Not cured	7 (5·1)	3 (4·3)	4 (5·8)

*For one case the information was missing because the couple was lost to follow up.

Results

Table 1 shows the characteristics of couples randomised to the two groups. There was good comparability in terms of baseline characteristics of women and their partners, including age, weight, marital status, mean numbers of sexual intercourse during the 3 months before study entry, interval from last sexual intercourse, history of genital infections, including previous episodes of bacterial vaginosis in women and urethritis in men. Further, the use of contraceptive methods was similar in women randomised to clindamycin and in the placebo group.

No important difference emerged between the study groups in self reported numbers of sexual intercourse during the study period. Two women reported a new untreated partner during the follow up period.

Table 2 shows the frequency of "cure" 7 days after start of treatment with clindamycin vaginal cream. Overall, 131 women out of the 139 who entered the study were cured (94·2%, lower 95% confidence interval 79·8, based on Poisson's approximation). There was no difference in the cure rate among women whose

Table 3 Reasons for withdrawal from study—Italy, 1994–5

Reason	Partner's treatment: Clindamycin No (%)	Partner's treatment: Placebo No (%)
Lost to follow up	6 (8·7)	3 (4·3)
Protocol violations:	15 (21·7)	19 (28·6)
The partner did no take all the drugs	12 (17·6)	15 (21·4)
Current antibiotic indication	2 (2·9)	2 (1·4)
More than 1 sexual partner during the study period	1 (1·4)	1 (1·4)
IUD used during the study period	—	1 (1·4)
Couple's request	1 (1·4)	1 (1·4)
Lack of efficacy	3 (4·3)	4 (5·8)
Partner's not serious medical event	1 (1·4)	2 (2·9)
Total	26 (37·7)	29 (41·4)

Table 4 Frequency of recurrence within 12 weeks after start of treatment according to the intention to treat and efficacy analysis and treatment allocation—Italy, 1994–5

Reason	Partner's treatment: Clindamycin No (%)	Partner's treatment: Placebo No (%)
Intention to treat analysis (whole series):		
Recurrence/persistence		
No	47 (68·1)*	49 (70·0)
Yes	22 (31·9)	21 (30·0)
Efficacy analysis (84 patients):		
Recurrence		
No	38 (88·4)*	32 (78·0)
Yes	5 (11·6)	9 (22·0)

*χ^2_1 = p not significant.

partner received clindamycin or placebo (χ^2_1 p = not significant). A total of 55 couples (26 in the clindamycin and 29 in the placebo group) withdrew from the study during the follow up period. The reasons are listed in Table 3.

Recurrence rate was similar in the two groups 4 weeks after start of treatment. According to the intention to treat analysis recurrence/persistence was observed in nine (13·0%) out of the 69 women whose partner received clindamycin and in eight (11·4%) out of the 70 who received placebo.

Table 4 shows the frequency of recurrence at 12 weeks according to the intention to treat analysis. Of the 69 women whose partner received clindamycin, 22 (31·9%) reported "recurrence" or persistence. The corresponding number was 21 (30%) out of the 70 women whose partner received placebo.

Of the 84 couples in which the woman was cured at the first week's visit and who completed the study, there were five recurrences (11·6%) among the 43 women whose partner received clindamycin and nine (22·0%) of the 41 whose partner received placebo (χ^2_1 p = not significant).

No difference emerged between the two groups in the recurrence rates at 4 and 8 weeks according to the intention to treat analysis (data not shown).

Local burning was reported by two women after treatment with clindamycin vaginal cream. Gastrointestinal symptoms were reported by seven men randomised to clindamycin and four randomised to placebo.

Discussion

Before discussing the results of this study potential limitations should be considered. The first is the large number of couples who withdrew from the study. However, the dropout rates and the causes for withdrawal were similar in the two groups. Another potential limitation is the small sample size. In fact, we were able to identify only a decrease in the frequency of recurrence in the partner's treatment group of 20%, to detect a difference of 10% in the recurrence rate the study would have to include about 600 patients.

To take these limitations into account and obtain a conservative evaluation of treatment efficacy, we have presented the intention to treat analysis that considers as treatment failures all subjects for whom no information on recurrence was available. We also decided to present the main analysis according to the intention to treat modality since we were interested in assessing the efficacy of male treatment in routine clinical practice. However, results were similar when the analysis included only couples who ended the study and respected the protocol. Other bias should not markedly affect the results. The same treatment schemes and criteria for assessing response were used in the collaborating centres. The clinicians were blind to the study treatment.

The cure rate of bacterial vaginosis after 1 week's vaginal treatment with clindamycin was high, about 95%. This is consistent with, or even better than, the results of previous studies with this drug in bacterial vaginosis. For example, in a large international study conducted in Germany, Austria, and Switzerland, comparing oral metronidazole and vaginal clindamycin and including more than 400 women with bacterial vaginosis, the cure or improvement rate 1 month after therapy was 83% in the clindamycin group.[16] Other studies reported response rates ranging from 60% to 95%.[6 17–20] Some of the differences may be attributable to different criteria for diagnosis of bacterial vaginosis and different concentrations of clindamycin in the vaginal cream, lower concentrations being associated with lower cure rates.

Few studies have analysed the effect of treatment of the sexual partner of women with bacterial vaginosis. The results are controversial.[8–12] No effect of male treatment with metronidazole on the presence of *Gardnerella vaginalis* emerged in a study including about 80 couples.[10] Likewise, there was no difference in symptomatic improvement, clinical cure rates, or culture results between women with bacterial vaginosis whose partners were treated with either tinidazole or placebo in a study including 250 couples in Thailand.[9] One large trial suggested that male treatment may reduce the recurrence rate.[11]

In this study we used clindamycin instead of metronidazole or its derivatives. Male treatment did not markedly reduce the recurrence rate of bacterial vaginosis. As previously discussed, owing to the low power of this study we were able to identify a marked difference in the recurrence rate between the two groups, although less marked reduction (as for example of about 10%) may have clinical relevance.

With regard to safety, the treatment was generally well tolerated. The frequency of adverse events was higher in the placebo group

than in the clindamycin group. Gastrointestinal disorders, the most common adverse events of oral clindamycin, were only slightly more frequent in the clindamycin group than in the placebo group.

In conclusion, this study confirms that vaginal clindamycin is effective and safe in the treatment of bacterial vaginosis. The findings, however, give no support to the suggestion that male treatment markedly reduces the short term recurrence rate.

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