Lactic acid gel versus metronidazole for recurrent bacterial vaginosis in women aged 16 years and over: the VITA RCT

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Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

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Scientific summary

The VITA RCT

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Scientific summary

Background

Bacterial vaginosis affects 30–50% of women at some time in their lives and is a distressing condition that is associated with potentially serious comorbidities. Current antibiotic treatments, such as metronidazole (Flagyl, Sanofi), are usually effective, but they can result in side effects, and recurrence is common. The metronidazole Versus lactic acId for Treating bacterial vAginosis (VITA) trial aimed to investigate whether or not lactic acid gel is clinically effective and cost-effective for the treatment of recurrent bacterial vaginosis compared with metronidazole.

Objectives

The primary objective was to determine whether or not intravaginal lactic acid gel is better than oral metronidazole for symptomatic resolution of recurrent bacterial vaginosis.

The secondary objectives were to:

- compare the time to first recurrence of bacterial vaginosis symptoms
- compare the frequency of bacterial vaginosis episodes over 6 months
- compare the frequency of bacterial vaginosis treatments required over 6 months
- compare microbiological resolution of bacterial vaginosis on microscopy 2 weeks after presentation
- compare the time to resolution of bacterial vaginosis symptoms
- compare the tolerability profiles of lactic acid gel and metronidazole
- compare adherence to lactic acid gel and metronidazole
- compare acceptability of the use of lactic acid gel and metronidazole
- determine the prevalence of sexually transmitted infections at baseline and week 2
- compare quality of life (measured using the Short Form-12 items health survey)
- compare the cost-effectiveness of using lactic acid gel with that of using metronidazole.

Methods

Trial design

This was an open-label, multicentre, parallel-arm, randomised (1 : 1) controlled trial.

Recruitment and follow-up

One general practice and 19 sexual health outpatient clinics in the UK recruited participants. Treatment was for 7 days, with follow-up taking place 2 weeks, 3 months and 6 months after randomisation.

Eligibility criteria

Inclusion criteria were women aged $\geq$ 16 years with a clinical diagnosis of bacterial vaginosis based on patient-reported symptoms and a history of one or more bacterial vaginosis episode(s) within the past 2 years that had resolved with treatment. Participants had to be willing to use the study treatment, take their own vaginal samples, avoid vaginal douching during the treatment, provide their contact details for follow-up, be able to complete a web-based questionnaire, avoid sexual intercourse or use effective contraception for the 7-day duration of the study treatment, and provide written informed consent. Exclusion criteria were contraindications or allergy to lactic acid gel or metronidazole tablets; pregnancy

or breastfeeding; currently trying to conceive; use of oral antibiotics (other than the study treatment) or antifungal agents concurrently within the last 2 weeks or planned use within the next 2 weeks; use of topical vaginal antibiotics, antifungals or acidifying products (other than the study treatment) concurrently within the last 2 weeks or planned use within the next 2 weeks; previous participation in the study; and concurrent participation in another trial involving an investigational medicinal product.

Study treatment

The two study treatment arms were:

- lactic acid gel (intervention) – 5 ml of gel inserted into the vagina before bedtime each day for 7 days
- metronidazole tablets (control) – 400 mg taken orally twice per day, approximately 12 hours apart, for 7 days.

Outcome measures

The primary outcome measure was participant-reported resolution of bacterial vaginosis symptoms at week 2.

The secondary outcomes were:

- time to first recurrence of bacterial vaginosis symptoms, as reported by participants
- number of participant-reported bacterial vaginosis episodes over 6 months
- number of participant-reported bacterial vaginosis treatment courses over 6 months
- microbiological resolution of bacterial vaginosis on microscopy of vaginal smears taken at week 2 and analysed at a central laboratory
- time to participant-reported resolution of bacterial vaginosis symptoms
- tolerability of lactic acid gel and metronidazole assessed by participant reporting of side effects (including nausea, vomiting, taste disturbance, vaginal irritation, diarrhoea and abdominal pain) and by participant interviews
- participant-reported adherence to treatment
- acceptability of treatments via qualitative assessment in a subgroup of participants
- prevalence of concurrent sexually transmitted infections (gonorrhoea, chlamydia and trichomoniasis) from vaginal swabs taken at baseline and at week 2, and analysed at a central laboratory
- quality of life assessed by Short Form-12 items health survey at baseline, 2 weeks, 3 months and 6 months
- comparative cost-effectiveness of lactic acid gel and metronidazole.

Participant-reported outcome measures were collected via web-based questionnaires, with several reminders sent to encourage completion. During the later stages of the trial, a follow-up telephone call was attempted to collect key outcomes from the week 2 and 6-month questionnaires when these had not been completed.

Sample size

Assuming that 80% of participants receiving oral metronidazole would achieve resolution of symptoms, 1710 participants (855 in each treatment arm) were required for analysis to detect a 6% increase in response rate to 86% in those receiving lactic acid gel (risk ratio 1.08) at the 5% significance level (two sided) with 90% power. To allow for a loss to follow-up of 10% (i.e. non-collection of the primary outcome data), the target sample size was 1900 participants.

Randomisation and blinding

Participants were randomised 1 : 1 to lactic acid gel (intervention) or metronidazole (control). A minimisation algorithm was used with the following variables: site, type of site (general practice or sexual health clinic),

number of episodes of bacterial vaginosis in the previous 12 months (0, 1–3 or > 3) and whether or not they had had a female sexual partner in the previous 12 months (yes/no). Randomisation was via a secure web server created and maintained by the Nottingham Clinical Trials Unit.

Given that this was an open-label trial, there was no blinding to treatment allocation for participants, site research teams or the trial team. However, the central laboratory staff performing bacterial vaginosis microscopy and sexually transmitted infection testing were blinded to treatment allocation. In addition, the trial statistician remained blinded to treatment allocation until after database lock. Analyses requiring knowledge of treatment codes were conducted by an independent statistician. Data presented to the Trial Steering Committee were not split by treatment allocation.

Statistical methods

The primary approach to between-group comparative analyses was by modified intention to treat, that is analysis of all participants who were randomised without imputation of missing outcome data according to the treatment arm that they were allocated to irrespective of adherence. Sensitivity analyses were conducted to investigate the impact of missing data and adherence to treatment.

The primary outcome measure was evaluated using a generalised estimating equation for the binary outcome, which included the minimisation factors with site as a panel variable. The comparison of lactic acid gel with metronidazole was presented using the risk difference in the proportion of participants who reported symptom resolution at week 2, along with the 95% confidence interval. Planned subgroup analyses included determining whether or not treatment effectiveness differed according to the following subgroups: (1) presence of concomitant sexually transmitted infection, (2) confirmation of bacterial vaginosis by positive microscopy and (3) type of centre that the participant presented at. The analyses according to presence of concomitant sexually transmitted infection could not be conducted owing to the small number of participants with an infection; however, summary statistics were provided. The analyses by type of centre were also not conducted given that only one general practice and no gynaecology clinics took part. In addition, the following subgroup analyses for symptom resolution at week 2 were included: the number of episodes of bacterial vaginosis in the 12 months before baseline and the total time with bacterial vaginosis in the 12 months before baseline. Between-group treatment effects were provided for each subgroup, but interpretation of any effects was based on the treatment by subgroup interaction and 95% confidence intervals, estimated by fitting an appropriate interaction term in the regression models. Given that the trial was powered to detect overall differences between the groups rather than interactions of this kind, these subgroup analyses were regarded as exploratory.

Secondary outcomes were analysed using appropriate regression models dependent on data type (e.g. binary, continuous, count and survival), and included factors used in the minimisation and baseline value of the outcome when measured. The analyses of secondary outcomes were considered supportive to the primary outcomes, and estimates and *p*-values, when presented, were interpreted in this light.

Health economics

The health economic analysis explored the cost-effectiveness of the study treatments from an NHS perspective. Resource use data collected via participant questionnaires included information on treatment use, general practice visits, clinic visits and other health-care resource use to estimate the costs associated with administrating both treatments. Data from the Short Form questionnaire-12 items were converted to a preference-based Short Form questionnaire-6 Dimensions score to allow quality-adjusted life-years to be calculated. An overall cost per patient successfully treated at 2 weeks was calculated, along with a cost per quality-adjusted life-year at 6 months. The difference in cost and health outcomes was compared between the two treatments.

Qualitative data analysis

A subgroup of participants was consecutively sampled and interviewed to further explore the adherence, tolerability and acceptability of treatment. The target sample size was approximately 30 participants (15 from each treatment arm). Data were coded thematically, with the codes based on interview questions and emergent themes. Coded data were compared between participants in the same arm of the trial and between treatment arms, and synthesised using a framework approach.

Results

In May 2019, the Data Monitoring Committee reviewed unblinded trial data at a planned meeting. Its recommendation was that recruitment should be stopped because its opinion was that the research question had been answered with the number of participants recruited at that time. There were no concerns raised around any safety issues. To ensure that this was a robust decision, further analyses were conducted by an independent statistician and reviewed by the Data Monitoring Committee in June 2019. The recommendation of the Data Monitoring Committee, supported by the Trial Steering Committee, remained the same and recruitment into the trial was terminated on 28 June 2019.

Between October 2017 and June 2019, 518 participants were randomised and primary outcome data were available for 409 participants (79%; 204 in the metronidazole arm, 205 in the lactic acid gel arm). Participant-reported resolution of bacterial vaginosis symptoms at week 2 was higher in the metronidazole arm (143/204; 70%) than in the lactic acid gel arm (97/205; 47%) (adjusted risk difference −23.2%, 95% confidence interval −32.3% to −14.0%). Sensitivity analyses were supportive of this treatment difference.

Among the participants who had symptom resolution by week 2, data on whether or not they experienced a recurrence over 6 months were available for only 72 out of 143 (50%) participants in the metronidazole arm and 46 out of 97 (47%) participants in the lactic acid gel arm. These data indicated that 51 out of 72 (71%) participants in the metronidazole arm and 32 out of 46 (70%) participants in the lactic acid gel arm experienced a recurrence within 6 months, with median times to first recurrence of 92 days and 124 days, respectively. The number of bacterial vaginosis episodes within 6 months in participants for whom complete episode data were available (metronidazole arm: 48/143, 34%; lactic acid gel arm: 29/97, 30%) was similar between arms (both had a median of one episode and maximums of six episodes in the metronidazole arm and 10 episodes in the lactic acid gel arm) (adjusted incidence rate ratio 0.97, 95% confidence interval 0.56 to 1.69). For those resolving by week 2, the median number of bacterial vaginosis treatment courses received between week 2 and 6 months was one in the metronidazole arm and one in the lactic acid gel arm (adjusted incidence rate 1.03, 95% confidence interval 0.53 to 2.01). However, this was based on participants with complete data (only 59 in the metronidazole arm and 35 in the lactic acid gel arm).

Microbiological resolution of bacterial vaginosis at week 2 in those in whom the condition was confirmed at baseline (based on microscopy of a vaginal smear) was higher in the metronidazole arm (59/77, 77%) than in the lactic acid gel arm (31/73, 42%) (adjusted risk difference −34.3%, 95% confidence interval −49.1% to −19.5%). The median time to symptom resolution was 14 days in both arms (adjusted difference 0%, 95% confidence interval −1.9% to 1.9%). A higher incidence of some side effects was reported in the metronidazole arm than in the lactic acid gel arm (nausea 32% vs. 8%, taste changes 18% vs. 1%, diarrhoea 20% vs. 6%, respectively). Adherence to treatment was good across both arms, with 316 out of 318 (99%) participants who returned a week 2 questionnaire reporting that they took at least some of their study treatment and 294 (92%) taking at least 85% of the course (metronidazole arm: 146/157, 93%; lactic acid gel arm: 148/161, 92%). Prevalence of sexually transmitted infections at both baseline and week 2 was very low.

The cost-effectiveness analysis found that lactic acid gel was less clinically effective than metronidazole in terms of participants with resolved symptoms at week 2 and that the average costs were higher (£86.94 in the metronidazole arm vs. £147.00 in the lactic acid gel arm). However, the sensitivity analysis indicated uncertainty around whether or not lactic acid gel was more or less costly than metronidazole. The cost–utility analysis suggested that lactic acid gel resulted in 0.003 fewer quality-adjusted life-years (95% confidence interval −0.013 to 0.009 quality-adjusted life-years) and was more costly by £58.60 (95% confidence interval −£55.05 to £185.32) than metronidazole at 6 months; however, the sensitivity analysis demonstrated that there was considerable uncertainty around these results.

In qualitative interviews, participants in general preferred lactic acid gel as a treatment, even if they perceived it to be less effective than metronidazole.

Conclusions

Participants with recurrent bacterial vaginosis had a higher response to treatment with metronidazole than with lactic acid gel at 14 days, but subsequent recurrence of symptoms over 6 months was common in both arms. Metronidazole is more likely to be cost-effective with lower associated resource use and higher efficacy than lactic acid gel, but there is uncertainty surrounding the resource use estimates. Participants interviewed in a qualitative substudy disliked taking a repeated course of antibiotics for bacterial vaginosis and in general preferred lactic acid gel, even if its short-term efficacy was lower than metronidazole.

Implications for health-care practice

The evidence suggests that intravaginal lactic acid may be an appropriate treatment option for some women with bacterial vaginosis. A discussion on its use should include information about lower short-term efficacy than metronidazole but fewer side effects, similar recurrence rates and its potential to avoid the use of antibiotic therapy.

Recommendations for research

1. In the absence of effective curative therapy, further investigation of non-antibiotic continuous or intermittent treatment regimens to control the symptoms of recurrent bacterial vaginosis is required to improve quality of life in this patient group.
2. Further analysis of vaginal samples would be useful to identify whether or not microbiological factors affect the short-term and long-term response to metronidazole or lactic acid gel in a subgroup of women with bacterial vaginosis.

Trial registration

This trial is registered as ISRCTN14161293.

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This report

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