Probiotics as Adjuvant Treatment for Bacterial Vaginosis

NCT03894813

2021-02-20

Study Protocol with SAP

This study was a single-centre, prospective, parallel-group, randomized, controlled study. Women who came to the gynaecological clinic of Peking University Shenzhen Hospital, China, between March 2019 and June 2019 with abnormal vaginal discharge symptoms were recruited, and eligible subjects were informed of the study protocol and enrolled in the study. The inclusion criteria were women aged between 18 and 65 years old, premenopausal women, women with a history of sexual activity, and women with a Nugent's Gram stain score of 7 or higher. The exclusion criteria were mixed vaginitis, such as vulvovaginal candidiasis (VVC), Trichomonas vaginalis (TV) infection, *Chlamydia trachomatis* (CT) infection or gonococcal vaginitis; planning for or being pregnant; breast-feeding; pelvic inflammatory disease; allergy to metronidazole; currently using antibiotics; long-term use of contraceptives or immunosuppressants or anaphylactic constitution; and a history of systemic organic diseases or psychiatric diseases. The study was conducted in accordance with the Declaration of Helsinki, was approved by the Medical Ethnic Committee of PKUSZH (with the Unique Protocol ID: PUshenzhenH2018-016) and was first posted on ClinicalTrials.gov (NCT03894813) on March 26, 2019. Informed consent was obtained from all subjects involved in the study.

The sample size was calculated based on the non-inferiority test (https://www.cnstat.org/samplesize/12/), which referred to Gregor Reid et al, who carried out studies with the same Lactobacillus strains administered orally to women with bacterial vaginosis (BV). The relevant parameters were determined as follows: test level α=0.05, test power 1-β=0.80, Pt=0.90, Pc=0.75, Nt:Nc=1:1, boundary value Δ= -0.0.068 (excellent), and Fisher's exact test. As a result, the sample size of each group was calculated as 50 patients, 100 patients in total. Considering a loss to follow-up rate of 20%, a sample size of 120 patients was finally determined, with 60 patients in each group.

After obtaining written informed consent, the participants were first asked to complete a questionnaire on demographic characteristics, reproductive health and sexual behaviour. They were subsequently randomly assigned to either the metronidazole group or the adjunctive probiotic group according to the random number table. The study was not blinded to the researchers or the patients. Starting from the enrolment day, the participants in the adjunctive probiotic group received orally administered probiotic drinks containing L. rhamnosus GR-1 and L. reuteri RC-14 ($\geqslant 1 \times 10^9$ CFU per day, for 30 days) and vaginally administered metronidazole suppositories (0.2 g per day, for 7 days), and the participants in the metronidazole group received metronidazole vaginal suppositories only. Clinical follow-up visits were scheduled at 30 and 90 days after starting treatment. The intervention products were dispensed by the investigator at the initial visit, and the compliance of participants was assessed by counting returned containers and filling out a questionnaire. The feasibility, acceptability and adherence to the administered products; vaginal symptoms; and

adverse events (AEs) were also assessed by self-report in medication diaries and questionnaires at follow-up visits. Therapy was initiated after the enrolment visit and suspended when menstruation began and continued immediately when it finished. Patients were asked to avoid sexual intercourse and vaginal douching during the first 7 days of treatment with metronidazole suppositories.

General information and clinical signs and symptoms of BV, including homogeneous and thin vaginal discharge, unpleasant odour (such as a “fishy” smell) and vulvar discomfort (such as itching or burning), were recorded at 0 day, 30 days and 90 days. The efficacy outcome was evaluated by the cure rate according to per-protocol (PP) analysis, which was the percentage of participants who did not present with BV (defined by Nugent score < 7) at any of the follow-up visits. Those with a Nugent score $\geqslant$ 7 in the 30-day follow-up was excluded from the trail, but when we evaluate the overall recurrence rate of the 90-day follow-up, these participants were still included in. At each follow-up visit, patients were requested to report any unexpected symptoms during the study period. AEs were recorded in the case report form (Table S1).

The diagnosis criteria of BV were based on Nugent Gram stain scoring of vaginal smears. The Gram-stained smear slides were examined microscopically, and the number of bacterial cells with different morphotypes was counted under 1000 × magnification. Each slide was identified according to Nugent score. A Nugent score of 0-6 was considered BV negative and of 7-10 was considered BV positive. The Gram stains were analysed in a double-blind manner by two experienced cytology technicians.

This study was a single-centre randomized controlled trial with two arms allocated at a ratio of 1:1. SPSS 13.0 software was applied to generate a random number table, and the random order was assigned depending on the order of enrolment.