

Acceptability and feasibility of Micralax[®] applicators and of methyl cellulose gel placebo for large-scale clinical trials of vaginal microbicides

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Objective(s): To evaluate the feasibility and acceptability of the Micralax[®] applicator and of methyl cellulose placebo gel for use in vaginal microbicide clinical trials.

Design: A two-centre prospective study following women for 2 months.

Setting: Two primary health care clinics in South Africa.

Patients, participants: Female volunteers (n = 28) 18 years or older who were HIV negative and had no clinically detectable genital tract abnormalities or reproductive tract infections.

Interventions: Participants used pre-filled Micralax[®] applicators to apply methyl cellulose gel every other day, as well as up to 1 h before to every episode of vaginal sex.

Main outcome measure(s): Consistency in the weight of gel dispensed per application; side-effects attributed to applicator or gel use; and acceptability of the applicator and of the gel.

Results: Over a 2 month follow-up period the 22 women completing the study reported no adverse events related to gel or applicator use. The Micralax[®] applicator proved acceptable. The gel was not too messy and did not reduce sexual frequency or pleasure. On average, the applicator dispensed 4.7 ml per use (close to the 4 ml planned).

Conclusions: The Micralax[®] applicator performs well as a delivery system for potential vaginal microbicides; and methyl cellulose is an appropriate placebo for future microbicide trials.

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AIDS 2001, **15**:1837–1842

Keywords: Applicators, clinical trials, placebo gel, vaginal microbicides

Introduction

Research on vaginal microbicides has progressed sig-

nificantly over the past decade. Currently, over 60 compounds are being evaluated [1]. Carrageenans, naturally occurring sulphated polymers extracted from

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Received: 21 December 2000; revised: 18 May 2001; accepted: 30 May 2001.

seaweed, show promise [2–5] and we are currently planning for large-scale effectiveness testing of one carrageenan formulation, Carraguard[®] (Clean Chemical Sweden AB, Borlange, Sweden). As this and other candidate microbicides advance through the product development pipeline, we wanted to evaluate and select a suitable applicator as well as an appropriate placebo for use in clinical trials.

In choosing an applicator, several criteria are important. The applicator should be inexpensive, simple to manufacture and fill, appealing to women, easy to use, and capable of delivering a consistent volume. Microbicides applicators should also be discreet and small enough to conceal while being stored, carried or disposed of. Typically, single-use applicators fit these criteria best. As compared to multi-use application systems, single-use applicators also avoid several potential problems with maintaining the sterility of the contents over time. During a literature search, we found no published studies of applicator feasibility or acceptability when used with vaginal microbicides.

Micalax[®] (Norden Pac International AB, Kalmar, Sweden) prefilled, single-dose, disposable plastic applicators (Fig. 1) are used in the UK and Sweden to deliver rectal laxatives. The applicators have a small bulb that users press between the thumb and forefinger to squeeze the contents out through the nozzle. They are inexpensive, easily manufactured and widely available. Micalax[®] applicators are smaller and more discreet than the plunger applicators typically used for spermicidal gels, for instance. To date, however, Micalax applicators have not been tested with vaginal products, and it is important to ensure that they are acceptable for this use. Moreover, at 34 000 centipoise, our candidate microbicide and placebo gels are more viscous than the laxative currently marketed in these applicators in Europe. We wanted to investigate whether the Micalax[®] applicator delivers a consistent volume of these gels, because if not then results from clinical trials using the applicator may not be valid. For instance, a truly effective microbicide might appear to be ineffective if too little is actually applied. Results of the present study would also indicate the correct

amounts of microbicides to package in each applicator at manufacture, considering that we wanted to test a dose of 4 ml of gel.

A secondary purpose of our study was to gain experience with methyl cellulose gel. This clear gel has the same viscosity, taste, smell and appearance as Carraguard[®], our candidate microbicide. Our proposed formulation consists of 2.5% methyl cellulose dissolved in water with 0.1% methyl paraben preservative, and sodium hydroxide to adjust the pH to 6. Methyl cellulose gel has no effect on either sperm motility or vaginal flora, and does not inhibit infection of another enveloped virus (herpes simplex type 2) in mice [6]. Other potential placebos showed some activity against HSV-2 in the mouse model (Carbopol[®] (Noveon Performance Materials, Cleveland, USA) and KY Jelly[®] (Johnsen & Johnsen Medical Inc., New Brunswick, USA), inhibited sperm motility (Carbopol[®]) or adversely affected lactobacillus and thus the vaginal flora (KY Jelly[®]) [6]. Methyl cellulose has also been studied previously in trials of vaginal products, both as a vehicle for the active ingredient and as a placebo [7–9]. It is also a component of many approved pharmaceuticals. This extensive track record gave us confidence that methyl cellulose gel would perform well as a placebo for our candidate vaginal microbicide.

Materials and methods

Our manufacturer filled Micalax[®] applicators with 7 ml (7.2 g) methyl cellulose gel. We estimated that this amount would deliver on average 4 ml of gel. Women in prior studies had indicated that the 5 ml of vaginal gel originally tested (using plunger applicators) were too messy [5,10].

We recruited women from family planning and general health clinics at two sites: Gugulethu (Cape Town) and Ga-Rankuwa (near Pretoria). This population had been selected for expanded safety trials of Carraguard[®] and data on the applicator combined with data from



Fig. 1. Micalax[®] applicator shown actual size. Total length, 10.5 cm; width at base, 2.9 cm; nozzle width at tip, 0.5 cm.

expanded safety trials will inform the feasibility of future effectiveness studies. Consenting volunteers were healthy, at least 18 years old, resident in the area for 12 months or more, HIV negative, willing to comply with the study protocol, and able to give informed consent. HIV positive women were excluded, as participants in this study were to be offered enrollment in the subsequent expanded safety trial, where seroconversion will be measured. All those testing HIV positive at screening chose to know their HIV results, received counseling from study staff and were referred to HIV primary care services for ongoing counseling and clinical management. We excluded women who: were pregnant or wanted to become pregnant during the study period, had had abortions or deliveries in the previous 6 weeks or genital tract surgery in the previous month, experienced vaginal bleeding with intercourse, had clinically detectable genital abnormalities or any reproductive tract infection, had an abnormal Papanicolaou test (class II and above), were allergic to latex, or were participating in another trial of a vaginal product. Women with asymptomatic syphilis or yeast infection, or a history of treated syphilis, were eligible for enrollment.

Participants gave informed consent at screening and again at enrollment. At every visit, all women received intensive condom counseling and free condoms (non-N9 lubricated latex condoms), along with intensive pre- and post-HIV test counseling, and treatment for curable sexually transmitted infections.

Participants were asked to apply gel every other day, whether or not they had intercourse, for the 2 month duration of the study. In addition, participants were asked to insert the gel up to 1 h prior to each act of vaginal intercourse. Study staff showed participants how to squeeze the gel from the applicator, starting by squeezing from the bottom (serrated edge) of the tube with their thumb and finger, and working upwards, so as to extrude as much gel as possible. Women received a supply of small sealable plastic bags, and were asked to return each used applicator sealed in an individual bag. We weighed each used applicator on calibrated scales (the identical model at each study site) to determine the gel volume actually dispensed. To reduce the possibility that evaporation could contribute significantly to measurement error, we weighed the applicators within a few days of their return to the clinic (at most 1 month after use).

At enrollment and each subsequent visit (14 days, 1 month, and 2 months) clinicians conducted pelvic speculum examinations and collected vaginal samples for Gram stain evaluation for bacterial vaginosis (Nugent criteria) [11] and detection of yeasts, and Diamond's medium culture evaluation for *Trichomonas*, and collected a cervical swab for testing for *Chlamydia* and *Neisseria gonorrhoea* (GenProbe Pace-2). Blood samples

were tested for HIV and syphilis at the original screening and the one-month visits. Clinicians also examined women at each visit for genital lesions.

At each of the three follow-up visits, women described any symptoms, and noted whether they attributed these symptoms to the applicator or gel. Women also evaluated the acceptability of the applicator and of the gel, answering a series of multiple-choice and open-ended questions about whether they felt comfortable using the applicator, how difficult it was to use, whether they were able to store their study applicators easily, and so on.

The Population Council's Institutional Review Board and the ethics committees at the University of Cape Town and Medical University of Southern Africa approved the study.

Results

Thirty-nine women were screened for the study, and 28 (13 from Gugulethu and 15 from Ga-Rankuwa) were eligible and agreed to participate. Seven women were ineligible due to positive HIV results, two did not complete the screening process, one was considered ineligible based on the staff member's assessment of her understanding of the study and one did not return for enrollment. Baseline characteristics of participants at enrollment are shown in Table 1. Twenty-two women completed 2 full months of follow-up. Of the six women who withdrew from the study prior to completing it, two moved out of the area or had work hours incompatible with study visits (after day 14 and month 1 visits); three cited partner concerns (after day 0 visits) and one reported labial itching 'possibly related' to the gel (although she had experienced this symptom prior to using the gel) (after month 1 visit). Women used an average of 44 applicators over the 2 month period (range, 3–72).

No serious adverse events occurred during the study, although 17 women experienced 22 mild or moderate adverse events. None of these events, however, were considered by the clinician to be 'probably related' to gel or applicator use.

The majority of the 22 (64%) participants liked the study product (gel and applicator), found the applicator appealing (54%), considered it easy to apply the gel (73%), and felt the gel was not 'messy' (60%). Sixteen (72%) women reported that being able to apply the gel up to 1 h before sex was acceptable, and 17 (77%) said that using the gel did not affect their frequency of sexual relations. Seven (32%) women attributed improvements in sexual pleasure to the gel, while one

Table 1. Selected baseline characteristics of study participants (n = 28) and reported acceptability of placebo gel and applicators (n = 22).

	n (%)
Participant characteristics	
Mean age (years)	28 (range, 18–42)
Married or with steady partner	24 (86)
Frequency of vaginal sex	1.6/week (range, 1/year–4/week)
Current contraceptive use	23 (82)
Type of contraception	
Injectables	19 (83)
Oral contraceptives	3 (13)
Female sterilization	1 (4)
Vaginal product use in last year	
Tampons	7 (25)
Agents to clean vagina	5 (18)
Agents to dry/tighten vagina	0 (0)
Condom use in the last year	11 (39)
Infections prevalent at screening	
Trichomoniasis	2 (7)
Bacterial vaginosis	11 (39)
Yeast infection	5 (18)
<i>Chlamydia</i> infection	1 (4)
Gonorrhea	1 (4)
Syphilis	4 (14)
Applicator and gel acceptability	
Overall opinion about the study product (gel and applicator)	
Liked it	14 (64)
Neutral	8 (36)
Disliked it	0 (0)
Messiness	
Not messy	7 (38)
Neutral	4 (22)
Somewhat messy	6 (33)
Very messy	1 (5)
No response	2 (2)
Application	
Very easy	16 (73)
Somewhat easy	1 (5)
Neutral	1 (5)
No response	4 (18)
Timing of gel application within 1 h before intercourse	
Wanted more time	6 (27)
Applying less than 1 h before was fine	16 (72)
Overall rating of study gel applicator	
Appealing	12 (54)
Neutral	9 (41)
Unappealing	1 (5)
Effect of gel on sexual pleasure	
Made sex much more pleasurable	6 (27)
Made sex somewhat more pleasurable	1 (5)
Had no effect	14 (64)
Made sex somewhat less pleasurable	1 (5)
Effect of study gel on the frequency of intercourse	
Increased frequency	5 (23)
Had no effect	17 (77)
Decreased frequency	0 (0)

(5%) reported corresponding reductions. Women also noted whether they tried to squeeze all the gel out of the applicator, or whether they had found the volume too much and therefore squeezed out only as much as they wanted. Of the 20 women who completed the study and responded to this question, 18 (90%) said they had tried to squeeze out all of the gel.

We discarded data on weights of the used applicators from the Ga-Rankuwa site because the weighing

procedures there were not adequately standardized with those from Gugulethu. Based on the 351 used applicators collected and weighed in Gugulethu, the gel volume dispensed per application weighed 4.6 g (SD, 0.87; range, 2.0–7.3 g), corresponding to approximately 4.7 ml (range, 2.1–7.5 ml). Most applicators (85%) delivered between 3 and 6 g (3.1–6.2 ml) of gel. Data on the amount of gel dispensed per applicator were normally distributed (Kolmogorov-Smirnov $P = 0.945$, data not shown). The mean gel volume dis-

pensed by each of 12 women (excluding one woman who did not return after enrollment) did not differ meaningfully across participants (Fig. 2). Every woman applied on average at least the 4 ml the applicator was intended to dispense.

Discussion

Early evaluation of applicators for vaginal products is important in order to interpret results from clinical trials, and to plan for successful distribution of a product once it is shown to be effective. An unappealing applicator could discourage women from using microbicides. The majority of participants in this study found the Micralax applicator to be acceptable. They found it easy to apply the gel, and applied a reasonably consistent amount, close to the 4 ml planned. They did not think this volume of gel was ‘messy,’ and the gel’s effect on sexual pleasure and frequency of sex was often positive.

No adverse events were considered ‘probably related’ to use of the methyl cellulose gel, bolstering the argument for selecting it as a placebo in future microbicide trials.

Cohort retention in this study was poor (6/28 or 21% did not complete the study). Based on this experience we have increased our emphasis on including partners in the decision to join the trial, offer partner counseling

if the woman wishes, and emphasize the importance of finishing the study during recruitment for our ongoing expanded safety studies. Data from that study will indicate whether it is possible to achieve adequate cohort retention for effectiveness trials.

Although not a primary outcome of the study, we note that condom use before the study was very low (39%). This low use persisted during the study period despite intensive condom promotion. Fewer than half (46%) of the 22 women completing the study reported that they used condoms, and nearly a quarter (23%) reported that they never used condoms, despite being sexually active. Together with high baseline prevalence of sexually transmitted infections, this low acceptance of condoms clearly demonstrates the need for a female controlled barrier method in this population of sexually active women.

Acknowledgements

The authors thank the Cape Town City Health Department for supporting microbicides research. We also thank C. Elias, E. Johansson, P. Kilmarx, R. McGuire, R. Roddy, K. Ryan and D. Taylor for their advice and guidance.

Sponsorship: Supported by the United States Agency for International Development.

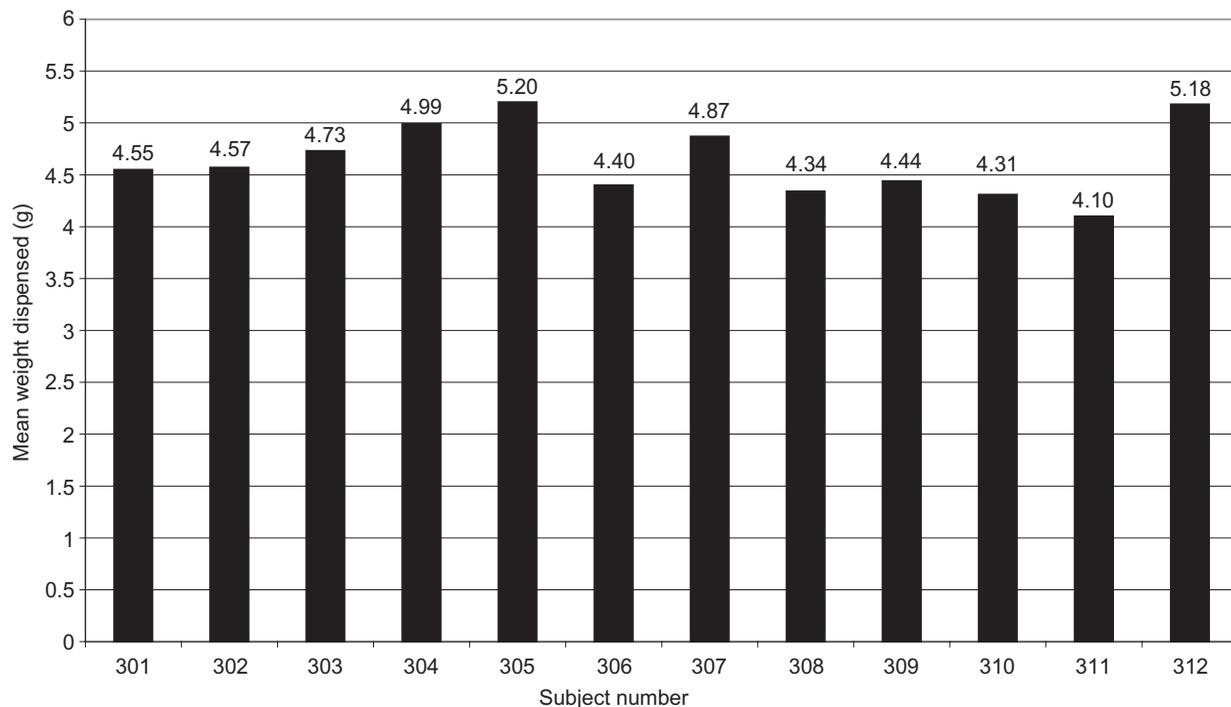


Fig. 2. Mean weight of gel dispensed by each of 12 participants (Gugulethu site).

References

1. Alliance for Microbicide Development. Microbicides in development – complete listing. Alliance for Microbicide Development Web site. Available at <http://www.microbicide.org/products%20in%20dev.htm>. Accessed November 22, 2000.
2. Pearce-Pratt R, Phillips DM. **Suphated polysaccharides inhibit lymphocyte-to-epithelial transmission of HIV.** *Biol Reprod* 1996, **54**:173–182.
3. Zacharopoulos V, Phillips DM. **Vaginal formulations of carrageenan protect mice from herpes simplex virus infection.** *Clin Diag Lab Immunol* 1997, **4**:465–468.
4. Elias CJ, Coggins C, Alvarez F, *et al.* **Colposcopic evaluation of a vaginal gel formulation of iota-carrageenan.** *Contraception* 1997, **57**:387–389.
5. Coggins C, Blanchard K, Alvarez F, *et al.* **Preliminary safety and acceptability of a carrageenan gel for possible use as a vaginal microbicide.** *Sex Trans Infect* 2000, **82**:480–483.
6. Maguire RA, Bergman N, Phillips DM. **Comparison of microbicides for efficacy in protecting mice against vaginal challenge with herpes simplex 2 virus, cytotoxicity, antibacterial properties and sperm immobilization.** *Sex Trans Dis* 2001; **28**:259–265.
7. Bell RJ, Permezel M, MacLennan A, *et al.* **A randomized, double-blind, placebo-controlled trial of the safety of vaginal recombinant human relaxin for cervical ripening.** *Obstet Gyn* 1993, **82**:328–333.
8. Elliott JP, Clewell WH, Rudin TG. **Intracervical prostaglandin E₂ gel: Safety for outpatient cervical ripening before induction of labor.** *J Reprod Med* 1992, **37**:713–716.
9. Sacks SL, Varner TL, Davies KS, *et al.* **Randomized, double-blind, placebo-controlled, patient initiated study of topic high- and low-dose interferon-alpha with nonoxynol-9 in the treatment of recurrent genital herpes.** *J Infect Dis* 1990; **161**: 692–698.
10. Coggins C, Elias CJ, Atisook R, *et al.* **A study of women's preferences regarding the formulation of over-the-counter vaginal spermicides.** *AIDS* 1998, **12**:1389–1391.
11. Nugent RP, Krohn MA, Hillier SL. **Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation.** *J Clin Microbiol* 1991, **29**:297–301.