Phase I safety & preliminary acceptability of nonoxynol-9 vaginal pessary as a vaginal microbicide in low risk women in Pune, India

S. Joshi, N. Joglekar, M. Ghate, J. Unni*, A. Risbud, M. Bentley**, M. Shepherd†, R. Bollinger† & S. Mehendale

National AIDS Research Institute (ICMR), *Hirabai Cowasji Jehangir Medical Research Institute, Pune, India, **Carolina Population Center, University of North Carolina, North Carolina & †Johns Hopkins University, Baltimore, USA

Received July 12, 2002

Background & objectives: Though nonoxynol-9 (N-9) is available in India as a spermicidal pessary, data on its safety as a potential microbicide among Indian women are not available. Nonoxynol-9 containing compounds have shown anti-HIV activity in in vitro studies and protection against cervical infections. Nonoxynol-9 is being extensively evaluated as a vaginal microbicide world-wide. We assessed the safety and preliminary acceptability of nonoxynol-9 pessary as a vaginal microbicide in women at low risk for human immunodeficiency virus (HIV) infection and sexually transmitted diseases (STDs).

Methods: Twenty three HIV seronegative women enrolled in the study were given Today™ pessarys containing 5 per cent of nonoxynol-9 for vaginal use at bedtime for 14 days. Colposcopy was done at enrollment and on day 14 and speculum examination on day 7 to assess the local toxicity.

Results: Most of the women (16/23, 69.6%) did not experience any symptoms of genital irritation. The remaining 7 (30.4%, 95% CI 11.6-49.2) women reported 11 episodes of mild irritative symptoms of short duration. On clinical examination, three adverse events were reported of which one could have been product related. Eight (34.8%) women showed willingness to use the product for protection against HIV transmission if it was approved.

Interpretation & conclusion: Nonoxynol-9 vaginal pessary was found to be safe and acceptable in once daily dose in low risk women after consecutive use for 14 days. Willingness for future use, if found safe and effective for HIV prevention was shown by 8 (34.8%) women.

Key words Colposcopy - microbicides - nonoxynol-9 - phase I

India is experiencing a rapid and extensive spread of the HIV epidemic and heterosexual transmission is reported to be the commonest route of its transmission1. Over 3.8 million people in India were living with HIV/AIDS at the beginning of the millennium; more than any other country in the world except South Africa2.

The efficiency of male to female transmission of HIV is 2.3-folds higher than that of female to male
transmission. It may be attributed to various anatomical, biological and sociological reasons. HIV infection in India is not only confined to the women with high risk behaviour but has also reached the low risk population and women are at a risk of HIV acquisition through sexual contact with their spouses practicing high risk behaviour or through sex work, respectively.

Although male condoms are widely available, and are well-recognized and effective means of preventing sexually transmitted diseases and HIV infection, their use requires the cooperation of the male partner. Female condoms are expensive and less readily available in the developing countries. This has prompted the search for safe and reliable female controlled methods for prevention of sexually transmitted diseases and HIV. Vaginal microbicides are products that are expected to inhibit the sexual transmission of HIV and other sexually transmitted pathogens. Potentially, these could be applied vaginally to prevent both male to female and female to male transmission. Therefore development of safe and efficacious vaginal microbicides is considered as an important research priority the world over.

Nonoxynol-9 is available in various formulations like gel, foaming pessary and vaginal film in the developed countries and has been extensively evaluated as a microbicide world-wide. Today™, a nonoxynol-9 formulation available in India as a spermicidal agent has not been tested for its toxicity and anti-STD/anti-HIV activity in systematic clinical trials in Indian women. Studies on nonoxynol-9 elsewhere in the world have suggested that in high and frequent doses it can cause vaginal and cervical irritation and possibly increase the risk of acquisition of HIV and sexually transmitted diseases.

Considering the spread of the HIV epidemic among women, a study was warranted to assess the safety of nonoxynol-9 in the Indian context. We conducted a phase I safety study of Today™, in Pune city in India, with the objectives of assessing the local toxicity of nonoxynol-9 pessary in low risk sexually abstinent and sexually active monogamous women, its preliminary acceptability in user couples and also compliance to the short-term (once daily use for 14 days) use schedule.

**Material & Methods**

This collaborative study between National AIDS Research Institute (NARI), Pune and Johns Hopkins University was approved by the Ethics Committee of NARI and the Institutional Review Board of Johns Hopkins University. Approval was also obtained from the Drug Controller General of India to conduct the Phase I study of N-9 as this is the first step in evaluating it as a microbicide.

The study was designed to enroll 5 women who would agree to be sexually abstinent during the study and 15 women who would agree to have sex at least twice a week with their husbands during the study period. Participating women were asked to use the product once daily for 14 consecutive non-menstruating days. At the screening visit, the objectives of the study and study procedures were explained to the participants and a written informed consent was obtained. Information related to demographic details, previous use of vaginal products, condom use and medical and obstetric history was recorded on a structured questionnaire. Blood samples were screened for HIV antibody and VDRL and urine was tested to rule out pregnancy. Pelvic examination was performed and samples were collected for Pap smear, wet mount, Gram stain, culture for gonorrhoea on modified Thayer-Martin medium (HiMedia, Mumbai, India) and chlamydia antigen detection test to rule out any pelvic infection.

Women who were HIV antibody and VDRL negative, had normal Pap smears, who were neither pregnant, nor lactating, who were not using any intra-uterine contraceptive device, had a steady sexual partner for the last six months, had no clinical or laboratory evidence of pelvic infection and who were willing to use the product daily for 14 days at bedtime, were called for enrollment 3 to 5 days after menstruation. Participants were offered a choice to enroll either into sexually active cohort or abstinent cohort.

At the enrollment visit, pelvic examination and colposcopy were conducted to rule out any base-line
clinical abnormality. The colposcopic evaluation was performed according to the recommended procedures\(^1\). Participants who were eligible for enrollment were given the vaginal pessarys containing 5 per cent of nonoxynol-9 and were shown a demonstration of product insertion and use with the help of a pelvic model. They were provided non-lubricated condoms and were also instructed on use of a daily diary during the study duration to record any side effects, symptoms and experiences related to acceptability of the product during its use.

The enrollment day was considered as day zero and the product was given to the participants on the same day after the enrollment eligibility was assessed. They were asked to use the product intravaginally once daily starting from day zero for 7 days and were called on day 7 (after completing 7 days product use) when they were evaluated clinically by speculum examination. The product use was continued for another 7 days and clinical examination and colposcopy was performed on day 14; colposcopic photographs were taken at enrollment as well as on the day 14 visit.

Preliminary acceptability was assessed at baseline on hypothetical product use and on days 7 and 14 after actual product use. Preliminary acceptability assessment after actual use included questions about the physical properties of the product such as colour, odour, and consistency and included several questions related to product characteristics, experience related to sexual intercourse and information on whether they would want to use the product for STD/HIV prevention if proven efficacious in future.

Criteria for discontinuation from the study were clinical diagnosis of any associated significant side effect, non-adherence to study protocol or unwillingness of the participant to continue further product use.

**Results**

Between January and July 1998, 37 women were screened for eligibility. Out of the 30 who were found eligible for the study, 23 (62.2%) were enrolled in the study and 7 were excluded at the time of enrollment. Condom use in the past six months was low (10.8%) in these women. The mean age of participants was 32.56±6.2 yr (range 23-45 yr). Of the total 23 women enrolled in the study, 16 women were enrolled in the sexually active cohort and 7 in the abstinent cohort.

Among the 23 participants enrolled, 16 (69.6%) did not complain of any symptom during the study period. Seven participants reported 11 episodes of mild symptoms as recorded in their daily diaries. They included increased frequency (n=1) and burning micturition (n=3), pain in the abdomen (n=1), headache and body ache (n=1), vulvar itching (n=1), burning of vagina (n=2), and folliculitis of vulva (n=1). One participant reported swelling of upper eyelids after accidentally touching of the eyelid after inserting the pessary. Folliculitis of the vulva resolved after a course of antibiotics for ten days and product use was continued during this period. The reported swelling of eyelids could have been a subjective feeling as this participant had accidentally touched her eyelids after inserting the pessary. This participant had no clinical findings and urine examination and kidney function tests were normal.

The local toxicity effects on clinical and colposcopic examination are shown in the Table. All the lesions resolved.

Colour, packing and smell was liked by 21 (91.30%), 18 (78.3%) and 17 (74%) women respectively and 22 (95.6%) women appreciated the portability of the product.

Among the active cohort (n=16), 3 (18.75%) reported leaking of the product before sex, two reported product leakage during sex and 7 (43.75%) after sex. Fifteen (93.75%) women reported that sexual intercourse was not interrupted for insertion of the pessary and 11 (68.75%) participants reported that the product use added to the sexual pleasure.

Of the 23 women enrolled in the study, 14 (60.9%) reported their willingness to use the product in future and these include 8 (34.8%) women who
showed their willingness for use of product in future for protection against HIV infection if it was approved. Of these 8 women, six were from the no symptom group and 2 women had reported 4 episodes of mild genitourinary symptoms (increased frequency, burning micturation, vulvar itching and pain in the abdomen). Three (13.04%) women showed willingness to use the product for contraception and lubrication respectively (Data not shown).

Among the 14 (3 sexually abstinent and 11 sexually active) women who reported their willingness for future product use, 11 (78.6%) did not complain of wetness with product use. Among the 11 sexually active women, who reported their willingness for use of the product in future, 8 (72.7%), 9 (81.8%) and 6 (54.54%) never experienced leaking of the product before, during and after sexual intercourse. Eleven of the 16 (68.75%) women in the sexually active group reported that the product use added to their sexual pleasure (Data not shown).

Discussion

The primary end point of this study was evidence of epithelial toxicity associated with the use of N-9 on cervicovaginal and vulvar epithelia as detected by pelvic examination and colposcopy. One limitation of our study was the difficulty in interpretation of quantitative data on a small number of participants, as has been reported by other investigators as well and inability to validate self-reports of product use. Although it is difficult to adopt specific measures to confirm the product use, we assessed the product use based on the amount of the product observed during pelvic examination and the responses of the participants at each clinic visit. In addition, the observation that the mean vaginal pH remained constant throughout the duration of the study gave an indication of regularity of product use by the women. These findings probably reflect last day’s use, however, only 4 of the 23 participants reported in their diaries that they had missed one dose but these individuals were considered adherent as per the protocol.

<table>
<thead>
<tr>
<th>Participant ID</th>
<th>Day of examination</th>
<th>Adverse event (type of lesion)</th>
<th>Cohort</th>
<th>Physician’s impression and outcome</th>
<th>Relation to product use</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP-20</td>
<td>7</td>
<td>Mild erythema and abrasion of vulva</td>
<td>Active</td>
<td>Participant was excluded from the study. She had used N-9 in the past without any side effects. Lesions resolved with local application of clotrimazole and beclomethasone cream</td>
<td>Not related to product use</td>
</tr>
<tr>
<td>NP-58</td>
<td>14</td>
<td>Mild erythema of upper lip of cervix</td>
<td>Abstinent</td>
<td>Had menstruation on the same day. Erythema might have been due to premenstrual congestion of the cervix. Lesion resolved without treatment after 7 days</td>
<td>Not related to product use</td>
</tr>
<tr>
<td>NP-22</td>
<td>14</td>
<td>Abrasion of cervix</td>
<td>Active</td>
<td>Resolved without any treatment</td>
<td>Speculum trauma that could be due to thinning of the epithelium related to product use</td>
</tr>
</tbody>
</table>

Table. Toxicity of nonoxynol-9 on clinical examination

JOSHI et al: SAFETY & PRELIMINARY ACCEPTABILITY OF NONOXYNOL-9 VAGINAL PESSARY AS A MICROBICIDE 155
No major side effects were found after once daily N-9 use for 14 days. The minor side effects subsided after follow up with or without treatment depending upon the condition. We could not determine whether the reported 11 episodes (47.8%) of irritative genitourinary symptoms were related to N-9 use as there were no placebo or condom-only arms in this study. It has been reported that women who were intensively monitored and were not using vaginal products other than tampons were more likely to report high levels of irritative symptoms. The abrasion seen in one participant in the active cohort was possibly caused by trauma by the speculum that could be due to thinning of the epithelium related to product use. This could be the only significant side effect possibly related to the product use. Spermicides have been previously also shown to cause mucosal erosion and ulceration, thereby increasing the risk of HIV-1 transmission. There are mixed reports about the safety and efficacy of nonoxynol-9.

Nonoxynol-9 was well accepted by the low risk trial participants and wetness, stickiness and leaking of the product was not perceived as a problem by most of the women.

One of the major findings of this study was that over one-third women reported that they would use the product if approved for protection against HIV/AIDS. This indirectly reflects their fear of getting infected with HIV from their sexual partners. We have reported a high prevalence of HIV among married monogamous women in STD clinics in Pune city. To conclude, nonoxynol-9 vaginal pessary available in India as a contraceptive was found to be safe and acceptable among the participating women. This study also demonstrated the felt need of the low risk women for a female controlled method to protect themselves against HIV and the need to initiate and strengthen research on vaginal microbicides in India.

Acknowledgment

The authors gratefully acknowledge Dr R.S. Paranjape, Officer-in-Charge, NARI for support and encouragement. Authors thank Dr U.P. Diwate, Dr E.K. Bharucha and Sh Dalvi of Hirabai Cowasji Jehangir Medical Research Institute, Pune for providing space in the hospital and laboratory support. The contribution of the HIVNET group consisting of K. Pardeshi, G. Kulkarni and R. Yelgate in clinic procedures and S. Kulkarni, V. Kale in laboratory procedures is acknowledged. This project was supported by funds from the National Institute of Allergy and Infectious Diseases (NIAID), NIH with technical assistance from Family Health International (FHI) and Indian Council of Medical Research, New Delhi.

References


Reprint requests: Dr S.M. Mehendale, Deputy Director (Sr. Grade), National AIDS Research Institute (ICMR) G-73, MIDC, Post Box No.1895, Bhosari, Pune 411026, India