Expanded Phase I safety and acceptability study of 6% cellulose sulfate vaginal gel

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Background: An expanded Phase I trial was performed to assess the safety and acceptability of 6% cellulose sulfate gel (CS) in comparison with K-Y Jelly.

Methods: Sexually abstinent (cohort I) and sexually active (cohort II) women in India, Nigeria and Uganda applied 3.5 ml of either 6% CS gel or K-Y Jelly for seven consecutive days. Safety was assessed by symptoms and signs (including colposcopy) of genital irritation, review of adverse events, and by changes in vaginal health as assessed by microscopy.

Results: One hundred and eighty women (90 on CS and 90 on K-Y Jelly) were enrolled. Baseline characteristics of women in both gel groups were similar. In cohort I, six (14%) women on CS and 12 (27%) on K-Y Jelly reported genital symptoms, two (in K-Y Jelly group) of whom withdrew from the study. New colposcopy findings or findings showing deterioration were detected in four (9%) women on CS and nine (21%) women on K-Y Jelly in cohort I. Two women on CS and three on K-Y Jelly in cohort II reported genital symptoms. Five women (11%) in each gel group in cohort II had new colposcopy findings or findings showing deterioration. The differences between the gel groups were not statistically significant. The majority of women had no problem with their assigned product.

Conclusion: A vaginal application of 6% cellulose sulfate twice daily for seven consecutive days is as safe and well tolerated as a similar regimen of K-Y Jelly. Further development of 6% CS for prevention of HIV and pregnancy is recommended.

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Introduction

Human immunodeficiency virus (HIV) and other sexually transmitted pathogens threaten millions of people worldwide. Globally, about 40 million people are living with HIV and in sub-Saharan Africa, women and girls account for 57% of all people infected with the virus [1]. Despite availability of effective methods for primary prevention of HIV infection (male and female condoms), such methods are often not feasible for the

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majority of women in developing countries. Topical microbicides may prove to be a critically important new method for women, and their partners, to protect themselves against HIV and other sexually transmitted infections.

Sodium cellulose sulfate (CS) is a long-chain sulfated polysaccharide under development as a topical microbicide and vaginal contraceptive. CS is a non-cytotoxic, anti-fertility compound with broad-spectrum antimicrobial activity. The contraceptive effects of CS have been demonstrated *in vitro* [2] and in rabbits [3]. CS mediates its contraceptive effects by stimulation of acrosomal loss, inhibition of hyaluronidase, and obstruction of sperm penetration into cervical mucus [3]. A vaginal contraceptive containing 100 mg CS and 230 mg nonoxynol-9 is licensed in Germany [4]. In-vitro studies of CS demonstrated potent inhibition of HIV, herpes simplex virus types 1 and 2, human papillomavirus and *Neisseria gonorrhoeae* and moderate inhibition of *Chlamydia trachomatis* [3,5] In a mouse model, CS was shown to significantly protect against *Neisseria gonorrhoeae* [6].

Several human trials have shown CS to be safe for topical application. In a 6-day safety study among US women, the safety of 6% CS was found to be similar to that of nonoxyl-9 (Conceptrol; Johnson & Johnson Corp., Maniti, Puerto Rico) and K-Y Jelly (Personal Products Company, Skillman, New Jersey, USA) [4]. In that study, CS was associated with less evidence of genital irritation than Conceptrol and K-Y Jelly. A penile tolerance study conducted in the US demonstrated that one out of 24 men in the CS group experienced tingling and slight stinging for a short period after 7 nightly applications compared with three out of 12 in the Conceptrol group [2].

To expand the clinical data for 6% CS among women in developing country settings, this study was conducted to determine the safety and acceptability of twice-daily vaginal applications of 3.5 ml 6% cellulose sulfate (CS) or 3.5 ml K-Y Jelly for seven consecutive days among sexually abstinent and sexually active women in India, Nigeria and Uganda.

Methods

This study was designed and sponsored by CONRAD (Arlington, Virginia, USA) and the World Health Organization (Geneva, Switzerland), and implemented at the Centre for Research in Reproductive Health (Sagamu, Nigeria), Department of Obstetrics and Gynecology, Makerere University (Kampala, Uganda) and the National Institute for Research in Reproductive Health (Mumbai, India). The study was conducted between December 2001 and July 2003. The study protocol was reviewed and finalized with study investigators at a meeting before commencing the trial. The study protocol was approved by scientific and ethics review committees at each implementing center and the World Health Organization.

The active product, CS, was studied at a concentration of 6% (60 mg/ml) and twice daily doses of 3.5 ml each, for a total daily dose of 420 mg. The vehicle contained preservatives (methyl- and propyl-paraben), a humectant (10% glycerin) and water. The inactive ingredients were grade materials listed in the United States Pharmacopeia–National Formulary. The inactive control product, K-Y Jelly, contained chlorhexidine gluconate, glucono-delta-lactone, glycerin, hydroxyethyl cellulose, methylparaben, purified water, and sodium chloride. CS and K-Y Jelly were similar in appearance and were supplied in identical, single-use applicators packaged in individual white wrappers.

Study design

This was a three-country, Phase I, randomized, double-blinded, comparative safety and acceptability study of 6% CS gel and K-Y Jelly, both administered vaginally in 3.5 ml doses. A total of 180 women were randomized to receive either 3.5 ml 6% CS or 3.5 ml K-Y Jelly applied twice daily for seven consecutive days.

The study was implemented in two consecutive cohorts, first among a group of women who were required to abstain from sexual intercourse (cohort I) and in a second group in which sexual intercourse was required (cohort II). All available cohort I safety data were reviewed before enrolling volunteers for cohort II in each site.

Study subjects

Study participants consisted of healthy, sexually abstinent and sexually active women, considered to be at low risk for HIV, recruited from family planning clinics and local communities in Kampala (Uganda), Mumbai (India), and Sagamu (Nigeria). Volunteers were aged between 18 and 50 years, had regular menstrual cycles or were on injectable contraceptives and amenorrheic for at least 6 months, were not at risk for pregnancy (because of tubal ligation, steroidal contraceptives, or abstinence if in cohort I), and were willing to adhere to the study protocol. Women were excluded from the study if they were known to have an allergy to any component of CS gel or K-Y Jelly or condoms (cohort II only), were currently pregnant or within 2 months from last pregnancy outcome, were known to abuse drug or alcohol, had evidence of an infection with *Trichomonas vaginalis*, Candidiasis or bacterial vaginosis which did not resolve with treatment or if they had gonorrhea or a chlamydial infection, had a history of herpes or condylomata within the past 6 months, or had non-iatrogenic abnormal colposcopy findings involving deep disruption of the genital epithelium at enrollment.

Study procedures

Participants were seen in three visits: screening, enrollment and a final visit. Volunteers were encouraged to attend unscheduled visits if they had a medical or any other problem related to product use. Potential volunteers were invited to attend a screening visit at each center. During the screening visit, the study was explained to the participants and informed consent obtained. Volunteers in cohort II were encouraged to inform their male partners about the study but partners were not consented for the study. Data on sociodemographic characteristics, and a medical history were obtained. A physical examination, including breast and pelvic examination, was done. A vaginal sample for wet mount and Gram stain and two endocervical samples for the detection of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were collected. Women who were diagnosed with *N. gonorrhoeae* or *C. trachomatis* were excluded from the study. Women who had an infection were treated according to the national guidelines of each participating country. A urine sample was taken for pregnancy testing. Volunteers were instructed to use no other intravaginal products, other than the study product, and to abstain from sexual intercourse for 72 h prior to enrollment until after the final visit if they were in the abstinent cohort (cohort I), whereas the sexually active cohort (cohort II) was required to have at least two acts of intercourse during product use from the period of enrollment to the final visit.

The enrollment visit was scheduled to fall between day 5 and 10 of the menstrual cycle. At enrollment, results from the screening visit were reviewed to confirm eligibility. Colposcopy was performed according to the WHO-CONRAD Colposcopy Manual [7]. Women with colposcopic findings involving deep disruption of the epithelium (ulcers, lacerations, or abrasions) were not enrolled. Eligible volunteers were randomized to receive either 3.5 ml 6% CS or 3.5 ml K-Y Jelly. They were provided with enough product to administer twice daily (at approximately 12-h intervals) for 7 consecutive days (total 14 applications). One extra applicator was given to facilitate having the final visit within 24 h after the last product application and for use in the event that a tube was damaged or lost. Product application was started either in the clinic or later at home. Cohort I volunteers were instructed not to have sexual intercourse during the 7 days of product use. Participants were given a diary card on which to record product insertion, and if literate, vaginal symptoms such as itching and burning and any other comments they had regarding the product. Cohort II volunteers were given male condoms and required to engage in a minimum of two acts of sexual intercourse during product use. Volunteers were instructed, if possible, to insert the product 5 to 15 min prior to intercourse in order to simulate the intended future use of the product, should it be marketed. However, participants were informed not to use the product more than twice daily regardless of the number of sexual acts. Each sex act was noted on the diary card in addition to any problem associated with the study product. Participants also recorded on the diary card any complaints, such as burning, itching or other adverse experience, of their partners as a result of product use. Volunteers were instructed to return for unscheduled visits if they experienced any medical problems during product use.

The final visit occurred within 24 h after the last product application. Specimens for pregnancy testing, wet mount, Gram stain and endocervical samples for the detection of *N. gonorrhoeae* and *C. trachomatis* were collected. Colposcopy was performed and any volunteers with findings that involved deep disruption of the genital epithelium were followed up within 48 h. A structured questionnaire to collect information on the acceptability of study products was administered. Acceptability assessment included questions on product satisfaction, partner involvement, experience with product during the trial, willingness to buy and use it in the future and whether to recommend it to others for pregnancy and/or disease prevention. Product compliance was assessed by interviewing volunteers, counting of used applicators and from information collected in the diary card.

Laboratory procedures

Wet mounts were examined for *Trichomonas vaginalis*, yeast and clue cells. A Gram stain was considered indicative of bacterial vaginosis if the Nugent score was ≥ 7; or in the range pH 4–6 and with discharge or odor. Amplicor *N. gonorrhoeae* and *C. trachomatis* co-amplification polymerase chain reaction (Roche Diagnostics, Basel, Switzerland) was performed according to procedures provided by the manufacturer.

Analysis of study outcomes

Data from all subjects who ever used study product (treated population) were included in the analysis of study outcomes. The main outcome was the number of women, in both cohorts, who experienced any signs and/or symptoms of genital irritation as reported by volunteers at any time during follow-up or as determined by naked eye examination of the genitalia, on colposcopy or microbiologic tests. The crude differences in the proportions of volunteers experiencing any study outcomes between the two product groups (CS and K-Y Jelly) and the 95% confidence intervals were calculated using *Z*-scores. All other adverse events were analysed in a similar manner. An adverse event was defined as any untoward medical occurrence in a participant during study participation. Adverse events were described as mild (minimal discomfort which did not interfere with normal daily activity), moderate (discomfort which interfered with normal daily activity) and severe (prevented normal daily activity). Colposcopic findings were graded for severity as mild (both epithelium and blood vessels were intact), moderate (epithelium or blood vessels were

sufficiently disrupted) and severe (involved deep disruption of the epithelium). Center-adjusted differences in proportions between the two product groups were estimated using generalized linear models (GLM), the models were fitted by assuming a binomial distribution for the error term with the identity link function [8]. The bootstrap technique was used to estimate standard errors.

Acceptability of the study product was assessed by a structured questionnaire. Percentage distribution of acceptability measures were calculated by center, cohort and study group. No tests of association between study groups and each of the acceptability measures were performed. All statistical analyses were performed using Stata 8 [9].

Results

Enrollment and eligibility

The first woman was enrolled on 16 December 2001, and the last woman completed the study on 4 July 2003. One hundred and seventy-six women were screened in cohort I (65 in Mumbai, 60 in Kampala and 51 in Sagamu) before enrolling a total of 90 women, 30 in each center. Similarly, 155 women were screened (45 in Mumbai, 68 in Kampala and 42 in Sagamu) to reach the enrollment target of 90 women in cohort II. Screening failures were due to medical problems (e.g. sexually transmitted infection, irregular menstrual cycles and chronic disease), unwilling to abstain from sex (cohort I only) and failure to return to the clinic during the screening period.

Among women enrolled in cohort I, 84 completed the study, two were lost to follow-up, two women on K-Y Jelly withdrew due to product-related adverse events, and two, one on CS and one on K-Y Jelly, withdrew due to early menstruation. In cohort II, 87 women completed the study, one woman on K-Y Jelly withdrew due to personal reasons, and two women in CS gel group did not use any study product due to early menstruation.

Baseline characteristics

Table 1 summarizes the baseline characteristics of the study participants. The mean age of women in cohort I was 31.9 (SD 8.4) years and 31.3 (6.5) years in cohort II. Over 60% of women in both cohorts had attended secondary school or higher education. However, in Kampala, a relatively low number of women had reached secondary school or higher education level (47% in CS and 40% in K-Y Jelly group in cohort I) compared with women enrolled in other centers (data not shown). Over 80% of the women in cohort I were in regular sex partnerships with the exception of women who were randomized to K-Y Jelly in Kampala (53%). Twenty percent of volunteers in Kampala had casual sex partners compared to none in Mumbai and 13% in Sagamu. Per protocol all women enrolled in cohort II were required to have a regular sex partner.

Although there were few differences between study groups within center and overall, there were clear differences between the centers (data not shown). The volunteers in the two African centers were more likely to have a lower education level, a casual sexual partner, and to use hormonal contraceptives than those from the

Table 1. Baseline characteristics of study participants.

	Cohort I				Cohort II			
	CS ($N = 45$)		K-Y ($N = 45$)		CS ($N = 45$)		K-Y ($N = 45$)	
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%
Age (years) mean (SD)	32	(6.9)	31.7	(8.2)	31.4	(5.6)	30.6	(6.3)
Education level[a]								
None	0	(0)	1	(2)	3	(7)	4	(10)
Primary	14	(31)	15	(33)	13	(29)	11	(26)
Secondary	24	(53)	22	(49)	23	(51)	24	(57)
Vocational	5	(11)	7	(16)	4	(9)	0	(0)
University/higher	2	(4)	0	(0)	2	(4)	3	(7)
Partner types								
Regular	38	(84)	37	(82)	45	(100)	45	(100)
Casual	5	(11)	3	(7)	N/A	N/A	N/A	N/A
None	2	(4)	5	(11)	N/A	N/A	N/A	N/A
Current contraception[a]								
Oral pills	12	(27)	10	(22)	21	(47)	15	(36)
Injectable	4	(9)	6	(13)	14	(31)	16	(38)
Tubal ligation	17	(38)	6	(13)	10	(22)	11	(26)
Abstinence	12	(27)	23	(51)	N/A	N/A	N/A	N/A
BMI (kg/m^2) mean (SD)	24.7	(5)	23.2	(4.4)	24.3	(4.3)	23.9	(4.3)
Previous pregnancies mean (SD)	4.1	(2.4)	3.7	(2.5)	3.3	(1.7)	3.6	(2)
Live births mean (SD)	3.5	(2.4)	2.9	(2.3)	2.8	(1.4)	3.1	(1.8)

Figures are numbers and percentages unless otherwise specified. [a]Numbers may not add up due to missing data. BMI, body mass index; CS, 6% cellulose sulfate gel; N/A, not applicable.

Indian center. They also had a higher number of previous pregnancies and live births.

Compliance

Being compliant was defined as applying the study product twice-daily for 7 consecutive days and having had at least two acts of intercourse if enrolled in cohort II. In cohort I, 42 of 45 (93%) women in the CS group used the product as instructed, and 41 of 45 (91%) in the K-Y Jelly group. Compliance in cohort II was 91% in the CS group and 100% in the K-Y Jelly group.

Genital symptoms

Safety data are summarized in Table 2. In cohort I, six (14%) women in the CS group reported a total of six genital symptoms and 12 (27%) women in the K-Y Jelly group reported a total of 16 symptoms. Corresponding figures in cohort II are two (5%) women reporting a total of two symptoms in the CS group and three (7%) women reporting three symptoms in the K-Y Jelly group. Individual symptoms reported by participants included vaginal discharge, bleeding, burning, itching, irritation, pain and non-menstrual bleeding. Genital symptoms were mild and possibly related to study products.

Microbiologic and gynecologic findings

New genital infections were diagnosed in two (5%) women in each gel group in cohort I, and in one woman in the CS gel group and three (7%) women in the K-Y Jelly group in cohort II. No woman had mixed genital infections. Infections detected included, in order of frequency, Candidiasis, *T. vaginalis* and bacterial vaginosis. Only two women, one in each gel group in cohort I, had new gynecologic findings and none in cohort II. One woman had cervical and vaginal bleeding and the other had adnexal and uterine tenderness.

Colposcopic findings

Four (9%) women in the CS gel group and nine (21%) women in the K-Y Jelly group had six and nine new or deteriorated colposcopic findings, respectively, in cohort I. In cohort II, five women in each group had five new or deteriorated colposcopic findings. Colposcopic findings were mild (except one finding in cohort I which was moderate) and included abrasions, ecchymosis, petechial haemorrhage, erythema and oedema. Differences in colposcopic findings between study groups in either cohort were not statistically significant.

Product acceptability

Product acceptability was assessed from data provided by study participants who completed an exit interview questionnaire (Table 3). In cohort I, two thirds of women who used CS and similar proportion of women who used K-Y Jelly found the gel very easy to use. Among women in cohort II, over 60% in both groups found their gel very easy to use. The majority of women in the study did not experience any problems with gel use. A total of 18 (eight on CS gel and 10 on K-Y Jelly) women reported product leakage. Over 80% of women in both gel groups in each cohort said that if the product were available, they would buy it for pregnancy protection, disease prevention, or both. Almost all women would recommend it to someone for pregnancy prevention, protection against sexually transmitted infections, or both.

Discussion

The results of this trial suggest that twice-daily vaginal application of 6% CS gel for seven consecutive days is as safe as a similar regimen of K-Y Jelly. Although there were

Table 2. Adverse events among product users, by cohort.

	Cohort I[a]				Cohort II[b]				Both cohorts					
	CS ($N = 44$)		K-Y ($N = 44$)		CS ($N = 43$)		K-Y ($N = 45$)		CS ($N = 87$)		K-Y ($N = 89$)		Adjusted[c] difference	
Event	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	*n*	*r*	δ	95% CI
Self-reported														
Genital symptoms	6	6	12	16	2	2	3	3	8	8	15	19	−0.076	(−1.116 to 0.964)
Non-genital symptoms[d]	2	4	3	4	3	3	3	4	5	7	6	8	−0.036	(−0.473 to 0.402)
New findings														
Microbiologic testing	2	2	2	2	1	1	3	3	3	3	5	5	−0.041	(−3.759 to 3.677)
Gynaecologic examination	1	2	1	2	0	0	0	0	1	2	1	2	[e]	
Colposcopic findings														
New or deteriorated	4	6	9	9	5	5	5	5	9	11	14	14	−0.032	(−0.190 to 0.126)
Adverse events combined	12	20	21	33	10	11	12	15	22	31	33	48	−0.135	(−0.266 to −0.004)

[a]Two subjects excluded due to loss of follow-up.
[b]Two subjects who did not use study product were excluded.
[c]Adjusted for center and cohort.
[d]Not related to product use.
[e]Model did not converge. CI, confidence interval; CS, 6% cellulose sulfate gel; *n*, number of subjects with at least one event; *r*, number of events; δ, difference.

Table 3. Product acceptability (responses from questionnaire).

	Cohort I[a]				Cohort II[b]			
	CS (*N* = 44)		K-Y (*N* = 43)		CS (*N* = 43)		K-Y (*N* = 45)	
	n	%	*n*	%	*n*	%	*n*	%
Insertion of gel								
Very easy	29	(66)	30	(70)	27	(63)	28	(62)
Easy	15	(34)	13	(30)	15	(35)	17	(38)
Neutral	0	(0)	0	(0)	1	(2)	0	(0)
Felt gel after insertion								
No	22	(50)	16	(37)	18	(42)	15	(33)
Yes	22	(50)	27	(63)	25	(58)	30	(67)
Description of gel feeling								
Very pleasant	4	(18)	5	(19)	4	(16)	5	(17)
Pleasant	8	(36)	16	(59)	17	(68)	22	(73)
Neutral	9	(41)	5	(19)	4	(16)	3	(10)
Unpleasant	1	(5)	1	(4)	0	(0)	0	(0)
Any smell with gel								
No	38	(86)	37	(86)	41	(95)	39	(87)
Yes	6	(14)	6	(14)	2	(5)	6	(13)
Description of smell								
Very pleasant	1	(17)	1	(17)	1	(50)	0	(0)
Pleasant	0	(0)	1	(17)	0	(0)	4	(67)
Neutral	3	(50)	4	(67)	1	(50)	2	(33)
Unpleasant	2	(33)	0	(0)	0	(0)	0	(0)
Any problem with gel								
No	38	(86)	33	(77)	36	(84)	44	(98)
Yes	6	(14)	10	(23)	7	(16)	1	(2)
Discussed gel use with partner								
No	13	(30)	16	(37)	N/A	N/A	N/A	N/A
Yes	31	(70)	27	(63)	N/A	N/A	N/A	N/A
Would buy gel for pregnancy and STI protection								
No	6	(14)	3	(7)	3	(7)	4	(9)
Yes	38	(86)	40	(93)	40	(93)	41	(91)
Would recommend gel for pregnancy and STI protection								
No	0	(0)	1	(2)	1	(2)	1	(2)
Yes	44	(100)	42	(98)	42	(98)	44	(98)

[a]Excludes two volunteers lost to follow-up and one who did not complete questionnaire.
[b]Excludes two volunteers who did not use study product. N/A, not applicable (partners in cohort II were informed about product use). CS, 6% cellulose sulfate gel; STI, sexually transmitted infections.

differences between centers, a heterogeneity test between centers and cohorts was not significant. These results are similar to those obtained from a previous study of 6% CS in the USA [4]. Although that study involved a smaller number of volunteers and used a different dosage and administration schedule, there was also less evidence of genital irritation in the CS group compared with K-Y Jelly. Our study provides further evidence that K-Y Jelly may be more irritating to the vagina in comparison with CS. In this and previous CS studies, only one woman discontinued gel application due to CS-related adverse events. Results are unlikely to be due to bias because the trial was randomized, double-blinded and identical applicators and packaging for the study products were used.

Acceptability of either CS gel or K-Y Jelly was a secondary endpoint. A small number of volunteers reported product leakage. Product leakage may influence acceptability and reduce overall use-effectiveness. The extent to which product leakage may affect product acceptability should be explored in qualitative research. Despite this, the results show that both CS gel and K-Y Jelly were well tolerated by most participants. In the previously mentioned 6-day study in the USA, only half of the women reported they would buy the product if available [4]. The authors concluded that the acceptability may have been low because about half of the volunteers were using permanent contraception and thus, not at risk for pregnancy. In the current study, only 38% subjects were using a permanent contraceptive method.

As this study was implemented in three different centers, two in Africa and one in South- Asia, the study population consisted of women from diverse ethnic and cultural backgrounds. Thus safety and acceptability results from this trial may be generalizable to women in other developing countries.

In conclusion, the results of this study suggest that 6% CS gel may be as safe and well tolerated as K-Y Jelly, which is marketed in most parts of the world. Research on further clinical development of 6% cellulose sulfate is warranted.

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