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Contraception 77 (2008) 191 – 194

Contraception

Original research article

The effects of spermicides containing nonoxynol-9 on cervical cytology☆

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Received 11 October 2007; revised 29 October 2007; accepted 8 November 2007

Abstract

Background: This analysis was undertaken to compare the effect of the different dosages and formulations of spermicides containing nonoxynol-9 (N-9) on cervical cytology.

Study Design: A randomized trial was conducted at 14 sites in the United States to evaluate the effectiveness and safety of five spermicides containing N-9. This Papanicolaou smear analysis included the data from all participants who provided two Papanicolaou smear samples: at admission and after discontinuation of the product. The effects of the spermicides were evaluated by comparing the rates of alteration of cervical cytology between five study groups.

Results: A total of 640 women were included in this analysis. The majority of the study participants (>85%) had no change of their baseline Papanicolaou smear result. The rates of alteration of cervical cytology were similar among women using the three gels containing the different doses of N-9 and three different formulations containing the same dose of N-9. Our analysis found no association between alteration of cervical cytology and duration or frequency of use of the five study spermicides.

Conclusions: Exposure to different formulations and doses of spermicides containing N-9 is unlikely to influence cervical cytology.

Keywords: Spermicide; Noxynol-9; Papanicolaou smear; Cervical cytology

1. Introduction

Vaginal spermicides containing nonoxynol-9 (N-9) have been available without prescription in the United States for more than 50 years. A nonionic detergent, N-9 dissolves the lipid components in the cell membrane of spermatozoa and causes their death or inactivation. N-9 also disrupts the membrane of bacteria, viruses and epithelial cells. Its in vitro activity against HIV and other sexually transmitted infections (STI), reported in the past [1], has not been confirmed in more recent clinical trials. Indeed, frequent use may increase a woman's risk of HIV-1 infection by causing genital lesions [2–4]. These findings eliminated the potential role of N-9 in HIV prevention. However, a better understanding of the safety of N-9 is important, since a large number of spermicides containing N-9 are being used world wide for contraception. Moreover, a number of surfactants with similar mechanisms of action have been investigated for use as microbicides for their potential protective effect against HIV. Data from women using N-9 may be extrapolated to provide insight into the safety of these new products.

Numerous clinical trials have demonstrated that the frequent use of N-9 was associated with an increased risk of vaginal and cervical irritation [5,6]. Colposcopy or simple visual examination were used in most of these studies to evaluate genital toxicity of N-9. However, only few studies used a Papanicolaou smear to assess cytologic changes of the cervical epithelium. The following analysis of the Papanicolaou smear data was undertaken to compare the effect of the different dosages and formulations of N-9 spermicides on cervical cytology.

The views expressed in this manuscript do not necessarily reflect those of Family Health International or the National Institute of Child Health and Human Development.

☆ Support for this study was provided by Family Health International with funds from the National Institute of Child Health and Human Development contract number N01-HD-7-3271.

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doi:10.1016/j.contraception.2007.11.015

2. Materials and methods

A randomized trial was conducted at 14 sites in the United States between June 1998 and August 2002 to evaluate the effectiveness and safety of five N-9 spermicides. The study was approved by the ethical review boards at each site and at Family Health International. All participants signed written informed consent forms before enrollment. The study was monitored by a Data and Safety Monitoring Board. The admission criteria and study procedures for the randomized study have been described previously [7]. In brief, participants were randomized to use one of the five marketed N-9 spermicides for 7 months. The spermicides included Gels A, B and C, which contained 52.5, 100 and 150 mg of N-9 per dose, respectively, and a film and a suppository each containing 100 mg per dose. Follow-up visits were conducted at 4, 17 and 30 weeks after admission to the study. Follow-up procedures included review of the diaries of menstrual periods, sexual activity and use of contraception; collection of adverse event information and a pregnancy test. A Papanicolaou smear was routinely performed for each participant as part of the admission and discontinuation evaluation. Women with abnormal Papanicolaou smear results were not excluded from the study.

The population included in the Papanicolaou smear analysis consisted of all women enrolled in the main trial who provided two Papanicolaou smear samples: the first at admission and the second within 6 weeks after the woman stopped using the spermicide as her primary means of contraception.

All cervical cytology samples were centrally interpreted at Kyto Meridien Laboratories (New York, NY, USA) using the 2001 Bethesda System terminology [8]. The lab personnel were blinded to the treatment groups. We classified all cytologic results as normal or abnormal. Normal results were divided into two subcategories: within normal limits and benign cellular changes. The latter included the results consistent with infection and reactive changes. Abnormal results were divided into three subcategories. Each subcategory consisted of abnormal Papanicolaou smear results that require similar evaluation and follow-up according to the 2001 consensus guidelines for the management of women with cervical cytological abnormalities [9]. Thus, Subcategory I included all results consistent with low-grade squamous intraepithelial lesion (LGSIL) and atypical squamous cells of undetermined significance (ASCUS); Subcategory II included the results consistent with high-grade squamous intraepithelial lesion (HGSIL) and atypical glandular cells of undetermined significance (AGCUS) and Subcategory III included the results suggestive of invasive cancer.

We compared the effects of the spermicides by comparing the rates of alteration of cervical cytology among the study groups. We considered cervical cytology as altered if, during two consecutive examinations, the Papanicolaou smear: (1) progressed (the results either transformed from normal to abnormal category or shifted to a higher subcategory within the abnormal category as compared to the baseline), (2) regressed (the results either transformed from abnormal to normal category or shifted to a lower subcategory within the abnormal category as compared to the baseline) or (3) did not change (the results either remained in the same subcategory or shifted between the normal subcategories as compared to the baseline.)

Mantel–Haenszel tests were performed to examine possible associations between cytologic alterations and the amount and formulation of N-9. To test these hypotheses, we compared the three gel products, each containing different amounts of the active ingredient per dose, and the three different formulations (film, suppository and Gel B), each containing the same amount of N-9 per dose.

3. Results

From 1536 women enrolled in the main trial, 640 women (42%) had at least two Papanicolaou smears and, thus, were included in the Papanicolaou smear analysis. Along with many similarities (parity, marital status, level of education, contraceptive use, prior use of spermicides), a number of significant differences existed between the women who were included in the Papanicolaou smear analysis and the women who were not. The percentages of older women and of black women were higher in the Papanicolaou smear population ($p=.03$ and $p=.05$, respectively). Women in the Papanicolaou smear population had lower coital frequency in the month before admission than those who were excluded ($p<.001$).

Participants included in the Papanicolaou smear analysis were equally distributed between the five treatment groups and did not differ with regard to the main demographic and baseline characteristics (Table 1). Most women were single and had more than 12 years of education. At least half of the participants in each group reported using spermicides prior to the study. Papanicolaou smear abnormalities at baseline were seen in 8–13% of participants in each group.

Participants used the assigned spermicide an average of 2.2 times a week and for a mean of 190 days before providing their second Papanicolaou smear. There were no major differences in duration and amount of spermicide use between the study groups. The second Papanicolaou smear specimen was obtained a median of 6 days after the date the participant stopped using N-9 for contraception.

Most study participants (>85%) had no change between the first and second Papanicolaou smear results. The rates of alteration of cervical cytology, including progression, were similar among users of the three N-9 gels and three N-9 formulations (Table 2). The rates of progression were somewhat higher and rates of regression somewhat lower in the 100- and 150-mg gel groups, as compared with the