Effect of a pH-Balanced Vaginal Gel on Dyspareunia and Sexual Function in Breast Cancer Survivors Who Were Premenopausal at Diagnosis

A Randomized Controlled Trial

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OBJECTIVE: To assess whether a pH-balanced vaginal gel containing lactic acid is more effective than a placebo (lactate-free gel) in improving dyspareunia and sexual function among breast cancer survivors who were premenopausal at diagnosis and had dyspareunia after adjuvant chemotherapy.

METHODS: In a single-center, double-blind, randomized trial, a pH-balanced gel or placebo was administered three times per week at bedtime as well as during sexual intercourse for 8 weeks. The primary outcome was the improvement of dyspareunia measured by pain score of the Female Sexual Function Index after the treatment. Secondary outcomes included the total and individual domains of Female Sexual Function Index score, sexual dysfunction (a total Female Sexual Function Index score less than 25.0), vaginal pH, vaginal maturation index, and adverse events related to the intervention. A sample size of 47 per group was planned to achieve 80% power to detect a 19% difference in the primary outcome.

RESULTS: From October 2009 and March 2013, 167 women were screened and 136 were randomized: 69 to a pH-balanced gel and 67 to placebo. Baseline characteristics were similar in both groups. Although there was no difference between the two groups, both experienced a significant improvement of dyspareunia. The increase in median pain score from baseline was 1.2 in both groups (median [interquartile range] from 2.8 [2.0–4.0] to 4.0 [2.8–4.8] in the pH-balanced group and from 3.2 [2.0–4.0] to 4.4 [3.2–4.8] in the placebo group; all P<0.01). Overall Female Sexual Function Index score and the frequency of sexual dysfunction also did not differ between the two groups although there was a significant improvement. On the other hand, vaginal pH and vaginal maturation index were slightly but significantly improved only in the pH-balanced group. There were no severe adverse events in either group.

CONCLUSION: The pH-balanced vaginal gel is not superior to the placebo in improving dyspareunia and overall sexual function.


DOI: 10.1097/AOG.0000000000001988

Sexual dysfunction is a common problem among breast cancer survivors. It is estimated that 30–100% of women with breast cancer have one or more sexual problems in terms of desire, arousal, lubrication, orgasm, and dyspareunia after treatment. Studies show that sexual dysfunction is closely related to a reduced quality of life among younger breast cancer survivors, defined as aged 50 years or younger or premenopausal at diagnosis.
The etiology of sexual dysfunction is multifactorial, but breast cancer treatment can have a significant effect on body functions related to sexual function in younger breast cancer survivors. Chemotherapy can induce early onset of menopause, and the resultant hypoestrogenism and vulvovaginal atrophy cause diminished vaginal secretions and delay in the timing of lubrication during sexual intercourse, contributing to dyspareunia. Even in women who are still premenopausal after chemotherapy, dyspareunia can occur during endocrine therapy because tamoxifen acts as an estrogen antagonist in the vagina. Previous experience with dyspareunia may deter or prevent women from desiring, initiating, or responding sexually to their partner. Studies show that vaginal dryness and dyspareunia are strongly associated with overall sexual dysfunction among younger breast cancer survivors. Therefore, appropriate intervention for these vaginal atrophic symptoms may aid in ameliorating sexual dysfunction among younger breast cancer survivors.

Although local estrogen therapy is the most effective for vaginal dryness and dyspareunia, its use raises concerns about systemic absorption and possible stimulation of cancer recurrence; therefore, vaginal lubricants and moisturizers are recommended as first-line therapies in breast cancer survivors. Nonetheless, there are few clinical data on their efficacy. One randomized controlled study of 45 patients with breast cancer who experienced vaginal dryness and dyspareunia found that a polycarbophil-based moisturizer and a placebo preparation were equally effective in relieving symptoms. In a separate randomized, placebo-controlled study that included 86 women, a pH-balanced gel was more effective in relieving both dryness and dyspareunia. However, they did not use a validated questionnaire to evaluate dyspareunia and could not assess the influence of the control of dyspareunia on the improvement of other domains of sexual function.

Thus, well-designed studies using validated instruments are still needed to clarify whether vaginal lubricants or moisturizers with or without pH-balancing could improve dyspareunia and other domains of female sexual function. In the present randomized controlled trial, we aimed to use a validated questionnaire to assess the effect of a pH-balanced vaginal gel on dyspareunia and overall sexual functioning in younger breast cancer survivors.

MATERIALS AND METHODS

We conducted a prospective, double-blind, randomized controlled trial of Korean breast cancer survivors between October 2009 and March 2013 (registered at ClinicalTrials.gov; NCT00981305). The protocol was approved by the institutional review board (SNUH 0905-037-281), and written informed consent was obtained from all participants. Participants were identified during history-taking on a routine outpatient clinic visit for a gynecologic checkup in Seoul National University Hospital. Eligible participants were women who were at least 20 years old, diagnosed with primary breast cancer before menopause, received adjuvant chemotherapy, and who were sexually active, defined as having sexual intercourse at least once a month and who had symptoms of dyspareunia. Exclusion criteria were as follows: 1) initiation or discontinuation of tamoxifen within 2 months, 2) previous use of vaginal lubricants, 3) current symptoms of active vaginal infection, 4) tumor recurrence, and 5) chronic medical or psychological disorders that can affect sexual function.

After informed consent was obtained, participants were randomly assigned to either a pH-balanced gel or placebo group. The identical tubes containing gel with or without lactate (pH 4.0 and pH 7.2, respectively) were prepared by the manufacturer and labeled with sequential numbers according to the randomization code. Randomization was performed by the coordinating researcher (S.H.) through a website using a computer-generated randomized table in random block sizes of four and six with stratification according to postbreast cancer treatment menopausal status and tamoxifen treatment. Menopause was defined as the cessation of menses for at least 1 year, and the tamoxifen treatment was included as stratification variables together with the posttreatment menopausal status because tamoxifen acts as either an estrogen agonist or antagonist on the vaginal epithelium according to the menopausal status. The participants were instructed to administer 3 mL of gel with a provided vaginal applicator three times per week at bedtime and additionally to use it during sexual intercourse for 8 weeks. All participating participants and outcome assessors were masked to the treatment assignment until the end of the study.

At the beginning of the study, sexual function of each participant was measured by a validated Korean version of Female Sexual Function Index. The Female Sexual Function Index is a 19-item self-reported instrument used for assessing key dimensions of female sexual function over 4 weeks, with a total of six domains being analyzed. Each of the six specific domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) analyzed in the Female Sexual Function Index is scored on a scale ranging...
from 0.8 to 6.0 (satisfaction), from 1.2 to 6.0 (desire), or from 0 to 6.0 (other four domains) with higher scores indicating better performance. The total score, falling in a possible range from 2.0 to 36.0, was obtained by adding the six domain scores together. Sexual dysfunction is defined as a total score of Female Sexual Function Index less than 25.0.16

Before initiating treatment with the study drug, vaginal health conditions were evaluated by vaginal pH and vaginal maturation index. During pelvic examination, vaginal pH was assessed with a pH indicator strip. Vaginal smear was obtained from the lateral vaginal wall, and vaginal maturation index was scored under a light microscope by a single pathologist (S.P.). Vaginal maturation index was calculated with a sum of percentages of superficial cells, intermediate cells, and parabasal cells that were assigned point values of 1.0, 0.5, and 0, respectively (vaginal maturation index = 0 × % of parabasal cells + 0.5 × % of intermediate cells + 1.0 × % of superficial cells).17 After 8 weeks of treatment, the participants were reassessed in terms of Female Sexual Function Index, vaginal pH, and vaginal maturation index.

The primary outcome was the improvement of dyspareunia (change of Female Sexual Function Index pain score; higher scores indicate less pain) after the treatment. Secondary outcomes included the total and individual domains of Female Sexual Function Index score, sexual dysfunction, vaginal pH, vaginal maturation index, and adverse events related to the intervention. Adverse events were categorized as major or minor complications. Systemic reactions including hypersensitivity, severe inflammation, and complications need to be hospitalized were categorized to major complications. Local milder reactions such as itching, irritation, and discomfort were considered minor complications.

The sample size was calculated based on the previous study.13 According to PASS 2008 software, we estimated that at least 47 participants were needed in each group for an 80% power to detect a 19% difference in the primary outcome measure with a two-tailed type I error of 5%. Assuming a dropout rate of 30%, we consecutively recruited the study population until we had enrolled 136 participants.

We assessed all study outcomes except for adverse events by both an intention-to-treat analysis and a per-protocol analysis. For the intention-to-treat analysis, we applied a conservative imputation for all women with missing data at the endpoint (a worst-case scenario, i.e., no improvement after the treatment). Statistical analyses were performed using SPSS 17.0 for Windows. The normality of the data for continuous variables was assessed using the Kolmogorov-Smirnov test, and the Student t test or Mann-Whitney U test was used to compare continuous variables between the two groups. For the comparison of categorical variables between the two groups, we used χ² test. The paired t test or Wilcoxon signed-rank test was used to analyze changes in continuous variables between baseline and the endpoint in each group, and changes in the frequency of categorical variables were analyzed by McNemar χ² test. All statistical tests were two-tailed, and statistical significance was defined as a probability value of <.05.

RESULTS

Among the 167 women screened, 136 were randomly assigned to the pH-balanced gel (n = 69) or placebo group (n = 67) and included in the intention-to-treat analysis. Four participants voluntarily withdrew from study participation without any definite reason, and 19 were lost to follow-up. Four of the pH-balanced gel group and two of the placebo group discontinued further treatment (one of each group was related to complications including vaginal irritation or itching and the others were not related to complications). As a result, a total of 107 women were included in the per-protocol analysis. The flow of participants is presented in the Consolidated Standards of Reporting Trials diagram (Fig. 1).

The baseline clinical characteristics of all study participants are described in Table 1. In both treatment groups, approximately 70% of women were taking maintenance tamoxifen therapy and were postmenopausal. There was no significant difference in characteristics between the two groups.

The overall outcomes of the trial by the intention-to-treat analysis are presented in Table 2. The primary outcome, pain score of Female Sexual Function Index, significantly increased after 8 weeks of treatment in both groups, indicating an improvement of dyspareunia. The increase in median pain score from baseline was 1.2 in both groups (median [interquartile range] from 2.8 [2.0–4.0] to 4.0 [2.8–4.8] in the pH-balanced group and from 3.2 [2.0–4.0] to 4.4 [3.2–4.8] in the placebo group; all P < .01). However, no difference was observed between the two groups.

Secondary outcomes including the total and individual scores for the domains of Female Sexual Function Index score and the frequency of sexual dysfunction also did not differ between the two groups. However, a total Female Sexual Function Index score significantly increased, and the frequency of sexual dysfunction was significantly decreased after the treatment in both groups (P < .01 and P = .01, respectively). Increasing scores...
in other five domains of the Female Sexual Function Index were also observed, although the change of scores of desire and satisfaction domains was not significant in the pH-balanced gel group. With regard to vaginal health conditions, a significant improvement was observed only in participants who had used the pH-balanced gel; vaginal pH decreased significantly (median [interquartile range] from 6.5 [6.0–6.8] to 5.5 [5.5–6.1]; \( P < .01 \)), and vaginal maturation index also significantly increased (from 46.0 [43.5–50.0] to 48.5 [44.6–51.6]; \( P < .01 \)). There were no changes in the vaginal pH (from 6.0 [6.0–6.5] to 6.0 [6.0–6.5]; \( P = .85 \)) and vaginal maturation index (from 46.0 [44.5–48.0] to 46.0 [45.0–49.0]; \( P = .87 \)) in the placebo group. The result of the per-protocol analysis was similar to that the intention-to-treat analysis (data are not presented).

Table 1. Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Group (n=67)</th>
<th>Study Group (n=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.2±5.2</td>
<td>48.1±6.3</td>
<td>.26</td>
</tr>
<tr>
<td>Menopause*</td>
<td>50 (74.6)</td>
<td>51 (73.9)</td>
<td>.98</td>
</tr>
<tr>
<td>Parity</td>
<td>2 (0–5)</td>
<td>2 (0–3)</td>
<td>.72</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4±3.2</td>
<td>22.9±2.5</td>
<td>.31</td>
</tr>
<tr>
<td>Tamoxifen treatment</td>
<td>45 (67.2)</td>
<td>46 (66.7)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation, n (%), or median (range) unless otherwise specified.
BMI, body mass index.
* Defined as the cessation of menses for at least 1 year.

During the study period, some participants reported adverse events including vaginal itching and irritation (Table 3). However, all of them were minor complications and self-limited. There was no significant difference in adverse events between the two groups.

DISCUSSION

The present randomized controlled study found that both the pH-balanced vaginal gel and the placebo demonstrated an improvement in dyspareunia and overall sexual function in breast cancer survivors who were premenopausal at diagnosis. The pH-balanced vaginal gel is not superior to the placebo in this regard, but it did have better efficacy in improving vaginal pH and vaginal maturation index.

Our results are in line with the findings of the previous study evaluating the effects of the pH-balanced gel on vaginal atrophic symptoms in breast cancer survivors who experienced menopause after chemotherapy or endocrine therapy. However, in that study, the pH-balanced gel was more effective in relieving dyspareunia than the placebo.\(^\text{14}\) This discrepancy might be the result of differences in study design. First, we instructed participants to use gels during sexual intercourse in addition to use on a regular basis (three times per week) to assess whether the expected effect of the pH-balanced gel on dyspareunia is through improving vaginal health or just providing lubrication. Second, we measured
dyspareunia with a validated questionnaire instead of a visual analog scale. The Female Sexual Function Index is one of the most commonly used questionnaires to specifically examine sexual function and has been validated for women with a history of cancer. The pain domain of the Female Sexual Function Index is composed of three items of question about the frequency and level of superficial or deep dyspareunia. Therefore, the pain score of the Female Sexual Function Index could represent the comprehensive aspect of dyspareunia compared with a visual analog scale that measures just the level of maximal pain.

Based on our study results, the relief from dyspareunia by the pH-balanced gel might be the result of lubrication action rather than vaginal health improvement. Although the vaginal maturation index has been used as an objective measure to evaluate the effect of treatments on vaginal atrophy along with the vaginal pH in various clinical trials, its reproducibility is being questioned even with experienced cytotechnologists. In addition, studies have demonstrated that vaginal moisturizers that have an acidic pH can lower the vaginal pH to premenopausal levels, but are not able to increase the vaginal maturation index, which suggests that vaginal atrophy cannot be restored just by lowering vaginal pH without estrogen replacement. Therefore, the favorable change in vaginal pH and vaginal maturation index by the pH-balanced gel should not be overinterpreted as resolution of vaginal atrophy.

Another consideration is what extent dyspareunia and overall sexual dysfunction will be improved by vaginal gels. In the present study, the increase in median pain score from baseline was 1.2, representing that vaginal gels can relieve dyspareunia by as much as 20%. Therefore, women with severe dyspareunia may not receive a sufficient benefit from just using vaginal gels. Nonetheless, there were small but statistically significant increases in a total and other five domains of Female Sexual Function Index score after the treatments, which supports the previous findings that vaginal dryness and dyspareunia are strongly associated with overall sexual dysfunction among younger breast cancer survivors. Although the clinical significance of these changes is unclear, it can be estimated by comparing the frequency of sexual dysfunction before and after the use of vaginal gels. In Korean women, the optimal cutoff of defining sexual dysfunction is a total Female Sexual Function Index score of 25.0.

Table 2. Changes in Parameters After 8 Weeks of Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control (n=67)</th>
<th>Study (n=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain score</td>
<td>3.2 (2.0–4.0)</td>
<td>2.8 (2.0–4.0)</td>
<td>.87</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>18.9±5.0</td>
<td>18.5±4.6</td>
<td>.73</td>
</tr>
<tr>
<td>Desire score</td>
<td>2.4 (1.8–3.0)</td>
<td>2.4 (1.8–3.0)</td>
<td>.76</td>
</tr>
<tr>
<td>Arousal score</td>
<td>3.0 (2.4–3.6)</td>
<td>3.0 (2.4–3.6)</td>
<td>.89</td>
</tr>
<tr>
<td>Lubrication score</td>
<td>3.0 (2.4–3.9)</td>
<td>3.3 (2.7–3.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Orgasm score</td>
<td>3.6 (2.4–4.0)</td>
<td>3.2 (2.4–4.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Satisfaction score</td>
<td>3.6 (2.2–4.8)</td>
<td>3.6 (2.2–4.8)</td>
<td>.38</td>
</tr>
<tr>
<td>Sexual dysfunction §</td>
<td>58 (86.6)</td>
<td>66 (95.7)</td>
<td>.06</td>
</tr>
<tr>
<td>Vaginal pH</td>
<td>6.0 (6.0–6.5)</td>
<td>6.5 (6.0–6.8)</td>
<td>.17</td>
</tr>
<tr>
<td>VMI</td>
<td>46.0 (44.5–48.0)</td>
<td>46.0 (43.5–50.0)</td>
<td>.47</td>
</tr>
</tbody>
</table>

Table 3. Adverse Events in Participants

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Control Group (n=57)</th>
<th>Study Group (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Minor complications</td>
<td>7 (12.3)</td>
<td>7 (14)</td>
<td>1.0</td>
</tr>
<tr>
<td>Vaginal itching</td>
<td>5 (8.8)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Vaginal irritation</td>
<td>1 (1.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1 (1.8)</td>
<td>2 (4)</td>
<td></td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified.
NA, not available.

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population, the frequency of sexual dysfunction has decreased by 16% after the use of vaginal gels. Given the multifactorial etiology of sexual dysfunction, these improvements appear to be clinically meaningful. Therefore, vaginal gels may be a reasonable treatment option for sexual dysfunction among younger breast cancer survivors.

Nonetheless, it is difficult to solve sexual dysfunction only by providing vaginal lubrication. Recently, fractional CO₂ laser has emerged as a promising treatment modality to be able to restore vaginal mucosal structure to a premenopausal condition without estrogen therapy and has been reported to improve dyspareunia related to atrophy. It may be especially helpful for women with dyspareunia secondary to a loss of tissue elasticity as well as vaginal dryness. In addition, it should be kept in mind that vulvodynia or vaginismus may cause sexual pain. A recent randomized controlled trial has demonstrated that the application of lidocaine to the vulvar vestibule before vaginal penetration can effectively reduce sexual pain refractory to lubricants. Another prospective cohort study showed that a combination of pelvic floor muscle relaxation exercises, olive oil lubricant as a lubricant, and a polycarbophil-based moisturizer significantly improved dyspareunia and sexual function in women after adjuvant breast cancer treatment. Beyond that, various factors including lower perceived sexual attractiveness, fatigue, and the quality of the partner relationship may cause sexual dysfunction in young breast cancer survivors. Therefore, when these factors are present, it may be better to incorporate other therapeutic options into treatment than to continue to use them.

The present study has some limitations. First, the study was performed in a single institution and all participants were Korean women. Second, a mixed population of women was included in this study. Because the vaginal environment might be different according to the menopausal status or tamoxifen treatment, how women respond to gel might be different. However, the sample sizes, when stratified by menopausal status or by tamoxifen treatment, did not permit sufficient statistical power.

In conclusion, the pH-balanced vaginal gel is not superior to the plain lubricants in improving dyspareunia and overall sexual function among younger breast cancer survivors. However, we observed a significant improvement of female sexual function associated with dyspareunia by using vaginal gels. In view of multifactorial characteristics of dyspareunia and sexual function, an individualized approach should be recommended in younger breast cancer survivors.

REFERENCES