Treatment of Secondary Vestibulodynia with Conjugated Estrogen Cream: A Pilot, Double-Blind, Randomized Placebo-Controlled Trial

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Abstract

Objective: To assess the efficacy of conjugated equine estrogen cream in reducing dyspareunia associated with secondary provoked vestibulodynia.

Methods: We conducted a randomized, double-blind, placebo-controlled trial that included women with secondary provoked vestibulodynia. Participants were randomly allocated to daily application of conjugated equine estrogen cream on the vulvar vestibule (estrogen group) or daily application of a similar placebo cream (placebo group). All patients were evaluated before and after eight weeks of treatment, using a visual analogue scale for superficial dyspareunia (primary outcome), the McGill Pain Questionnaire for superficial dyspareunia, the Female Sexual Function Index for sexual satisfaction, and vulvoscopy for vestibular erythema.

Results: The targeted recruitment for this study was 44 women, but because of funding shortfalls recruitment was limited to 20 women. These 20 participants were randomly assigned to two groups of 10. Improvement of superficial dyspareunia on the visual analogue scale was not significantly different between the two groups (estrogen group: 27% improvement vs. placebo group: 3% improvement, $P = 0.29$). However, the use of conjugated equine estrogen cream was associated with a significant post-treatment improvement in superficial dyspareunia and in all three secondary outcomes ($P < 0.05$), whereas this was not the case with the use of placebo.

Conclusion: Daily application of conjugated equine estrogen cream to the vulvar vestibule could potentially reduce superficial dyspareunia in women with secondary provoked vestibulodynia, but a randomized trial with adequate statistical power will be required to demonstrate this.

Key Words: Women's health, dyspareunia, estrogen, randomized trial

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Résumé

Objectif : Évaluer l'efficacité de la crème à base d'œstrogènes équins conjugués pour atténuer la dyspareunie causée par la vestibulodynie provoquée secondaire.

Méthodologie : Essai randomisé à double insu avec placebo portant sur des femmes souffrant de vestibulodynie provoquée secondaire. Les participantes ont été placées aléatoirement dans le groupe A (application quotidienne de crème à base d'œstrogènes équins conjugués sur le vestibule vulvaire) ou le groupe B (application quotidienne d'une crème placebo d'apparence semblable). Tous les sujets ont été évalués avant et après huit semaines de traitement au moyen de quatre mesures validées : l'échelle visuelle analogique pour la dyspareunie superficielle (résultat principal), le McGill Pain Questionnaire pour la dyspareunie superficielle, le Female Sexual Function Index pour la satisfaction sexuelle et la vulvoscopie pour l'érythème vestibulaire.

Résultats : Le recrutement a été interrompu avant l'atteinte de la cible ($N = 44$). Vingt participantes (10 par groupe) ont été assignées aléatoirement à chaque groupe. L'atténuation de la dyspareunie superficielle selon l'échelle visuelle analogique n'était pas significativement différente entre les deux groupes (27 % contre 3 %, $P = 0,29$). Cependant, l'utilisation de la crème à base d'œstrogènes équins conjugués a été associée à une atténuation significative de la dyspareunie superficielle entre le début et la fin du traitement, ainsi qu'à une amélioration des trois résultats secondaires ($P < 0,05$), alors que la crème placebo n'a pas entraîné d'effet significatif.

Conclusion : L'application quotidienne de crème à base d'œstrogènes équins conjugués sur le vestibule vulvaire pourrait atténuer la dyspareunie superficielle, mais un essai randomisé d'une puissance suffisante sera nécessaire pour le confirmer.

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INTRODUCTION

First described as "hyperaesthesia of the vulva" by Thomas in 1880,[1] then named "vulvar vestibulitis syndrome" by Friedrich in 1987,[2] vestibulodynia is a complex vulvar pain disorder. In North America, up to 12% of women experience vestibulodynia.[3,4] Provoked vestibulodynia is considered the most common cause of superficial dyspareunia in premenopausal women, and 50% to 80% of cases develop after a period of pain-free intercourse (secondary vestibulodynia).[5–11] Vestibulodynia significantly affects women's sexual function and quality of life.[12,13]

Two criteria for the diagnosis of vestibulodynia have been established by Friedrich: severe pain on vaginal entry or touching of the vestibule and tenderness to pressure within the vestibule for at least six months.[1,9,14–17] Other manifestations include burning pain during gynaecological examination or with insertion of a vaginal tampon.[1,5,6,8,9,14]

Vestibulodynia predominantly affects Caucasian women aged 20 to 40.[4] According to the 2015 definition from the International Society for the Study of Vulvovaginal Disease, the International Society for the Study of Women's Sexual Health, and the International Pelvic Pain Society, no clear cause has been identified, but potential factors could be associated, such as other pain syndromes, genetic factors, hormonal factors, inflammation, neurological mechanisms, psychosocial factors, and structural and musculoskeletal factors.[18,19] Other hypotheses for etiology and risk factors for vestibulodynia have been studied, but none has been directly associated with the disorder.[8,9,19–21] Histopathological examination of the area affected by vestibulodynia may show a chronic and nonspecific inflammation.[1,9,20,22] It has been hypothesized that hormonal factors could be involved in the pathogenesis of vestibulodynia because estrogen receptors have been identified in the vulvovaginal area.[1,8,15–17,22–25] This hypothesis was the cornerstone of our study. Based on a previous six-week, double-blind, randomized trial involving 61 participants, intravaginal application of estrogen cream (3 g daily) was associated with a significant reduction in erythema and inflammation surrounding the Bartholin's glands, although no significant reduction in dyspareunia was found between the estrogen and placebo groups.[15]

ABBREVIATION

VAS Visual analogue scale

The objective of the current study was to assess the efficacy of an estrogen cream applied directly to the vulvar vestibule in reducing superficial dyspareunia associated with secondary provoked vestibulodynia.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial between September 2011 and March 2013 at the Centre Hospitalier Universitaire de Québec and Centre Médical Santé Femme (Québec City, QC). Written informed consent from each participant was obtained before randomization.

We recruited women aged 18 to 45 with secondary provoked vestibulodynia, superficial dyspareunia for at least 3 months, and moderate-to-severe pain during the swab test ($\geq$4/10 on a visual analogue scale). The swab test is performed by pressing a cotton swab on the vestibule and sliding it along the vestibular surface several times. Participants were required to use an efficient form of contraception, with a Pearl index of <10% (the use of condoms alone was not sufficient), to ensure that no pregnant woman would receive topical hormone therapy. Participants also were required to be in a heterosexual relationship with the partner physically present throughout the trial to permit intercourse. We excluded women with severe vaginismus, a history of sexual assault, immunodeficiency, active genital infection, and a known diagnosis of vulvar disease because these women may have had another etiology for their vestibulodynia. Women breastfeeding or with a contraindication to estrogen cream were also excluded, as were women using other forms of local therapy (e.g., local anaesthetic agents) or with a history of previous treatment for vestibulodynia. Women with primary vestibulodynia were not recruited because our study focused on secondary provoked vestibulodynia and its treatment.

Women with superficial dyspareunia who met the inclusion criteria were informed about the study, and if they agreed to participate, they were enrolled in the study at the time of the first consultation with one research nurse and two physicians at the Centre Médical Santé Femme. A second visit was scheduled 3 weeks later for randomization (visit 2). Subsequent follow-up visits were at 4 weeks (visit 3) and 8 weeks (visit 4) after randomization. Randomization was performed using a computer-generated randomization process in a 1:1 ratio. Equine estrogen was supplied by Pfizer Canada Inc. (Kirkland, QC). Tubes of cream (estrogen and placebo) were prepared and supplied by Gentès & Bolduc Pharmaciens (Québec City, QC). They