European Journal of Obstetrics & Gynecology and Reproductive Biology 234 (2019) 92–95

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Efficacy and safety of a non-hormonal intravaginal moisturizer for the treatment of vaginal dryness in postmenopausal women with sexual dysfunction

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ARTICLE INFO

Article history:
Received 25 June 2018
Received in revised form 11 November 2018
Accepted 27 December 2018

Keywords:
Menopause
Vulvovaginal atrophy
Vaginal dryness
Sexual dysfunction
Dyspareunia
FSFI
VHI

ABSTRACT

Objective: Evaluate the efficacy and safety of a non-hormonal intravaginal moisturizer on reducing the symptoms arising from vaginal dryness and sexual dysfunction.
Study design: A total of 37 postmenopausal women used a non-hormonal intravaginal Moisturizer (polycarbophil, butyl ester of a copolymer of methyl vinyl ether/ copolymer PVM/MA, 50% sodium lactate solution, and Carbopol) twice a week for 12 weeks. The vaginal moisture levels, volume of fluid, elasticity, and epithelium integrity were assessed using the Vaginal Health Index. Sexual function was measured using the Female Sexual Function Index questionnaire. All women were evaluated before starting treatment and at the 4th, 8th and 12th weeks of the study. At the end of the study, the patients analysed the treatment regarding to their satisfaction with the product, and its application system, their sense of well-being after using it as well as their perception bout the discharge of the moisturizer (if it run or was held by the vaginal mucosa).
Results: There was a significant improvement in the vaginal moisture, fluid volume, elasticity and epithelial integrity ($p < 0.001$). Sexual function improved in the total score and in all six domains ($p < 0.001$). More than 50% of all patients reported being very satisfied with the treatment and product application. The sense of well-being was considered very good by 51.4% of the participants and most (91.9%) indicated that the product did not leak and did not stick to the vaginal mucosa. No severe adverse events were reported.
Conclusion: Our study suggests that treatment with the non-hormonal intravaginal moisturizer is a safe and efficient therapeutic option for the improvement of vaginal dryness with encouraging benefits for the sexual function of postmenopausal women.

Introduction

The onset of menopause is accompanied by an increase in reported symptoms of vaginal dryness, soreness, irritation or itching, pain during and bleeding after intercourse. Collectively these symptoms represent vulvovaginal atrophy (VVA), a condition that affects 25–50% of postmenopausal women [1,2].

The main consequence of painful sexual intercourse is diminished desire and interest in sex [3], thereby affecting sexual intimacy negatively and the overall quality of life [4]. Indeed, in 2014, the REVIVE survey in the USA analyzed 3046 postmenopausal women with VVA symptoms and observed that the most common symptoms were vaginal dryness (55%) and dyspareunia (44%) and that VVA affected sexual pleasure in 59% of the participants [4]. The European REVIVE evaluated 3768 postmenopausal women and showed that VVA has a significant negative impact on the women's capacity to be intimate (62%), appreciate the sexual relation (72%), and to feel sexual spontaneity (66%) [5]. More recently, the Latin America VIVA-LATAM evaluated 2509 postmenopausal women and reported 57% of vaginal atrophy [6].

Although hormonal therapies based on the local or systemic administration of estrogen are efficient for the treatment of the symptoms associated with VVA in postmenopausal women, they are contraindicated in some cases such as women with vaginal/uterine bleeding and endometrial or breast cancer. Therefore, non-hormonal intravaginal moisturizers are indicated by several scientific societies as the first-line treatment to relieve the symptoms associated with VVA, including inadequate lubrication [7–9].

Non-hormonal intravaginal moisturizers are composed of polymers that provide bioadhesion and hydration due to the

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https://doi.org/10.1016/j.ejogrb.2018.12.040
0301-2115/

chemical properties of these components. They aggregate water molecules that, besides hydrating, provide a wide adhesive surface to contact mucin, the glycoprotein of the mucus, to which the polymers integrate resulting in adhesion to the mucosa [10]. Moreover, this association maintains the physiological vaginal pH thus avoiding the proliferation of fungi and undesired bacteria [1,11]. Although several non-hormonal intravaginal moisturizers are commercially available, little is known about their efficacy and their impact on sexual function and satisfaction as well as on women's well-being.

The present study evaluated the efficacy and safety of a novel non-hormonal vaginal moisturizer with a new association of polymers, in postmenopausal women with vaginal dryness, dyspareunia, and female sexual dysfunction.

Methods

Study design

We performed a prospective, open-label, controlled study to evaluate the efficacy and safety of a non-hormonal intravaginal moisturizer gel (Hidrafemme – Farmoquimica - Brazil) composed of polycarbophil, butyl ester of a copolymer of poly (methyl vinyl ether)/maleic acid (copolymer PVM/MA), 50% sodium lactate solution, and Carbopolon in the improvement of vaginal dryness and sexual dysfunction in postmenopausal women. All participants read and signed an informed consent form. The study was approved by the research ethics committee of the Universidade Federal de Minas Gerais (UFMG) under COEP-1379159.

Patients

A total of 48 healthy sexually active postmenopausal women, with at least one sexual intercourse per month, reporting vaginal dryness according to the Vaginal Health Index (VHI) [12], were selected to participate in the study. The study was conducted at the Clinic of Sexology of the Department of Gynaecology and Obstetrics — UFMG, Brazil, from January to May 2016. All participants were older than 40 years old, with at least one year since their last menstrual period, had a follicle-stimulating hormone level above 30 IU/L, estradiol levels below 40 pg/mL, and no previous history of reactions to the components of the non-hormonal intravaginal moisturizer. None had used intravaginal moisturizers or hormonal therapy in the previous three months, were smokers and had a previous history or visible evidence of chronic skin disease, genital herpes, vaginal infections, urinary tract infections, unbalanced endocrine system, hepatic disease, breast or endometrial cancer, previous oophorectomy and thromboembolic disease. Women reporting interpersonal relationship problems or those whose partners had sexual problems were not included in the study.

Evaluation and treatment

All women were instructed to use the non-hormonal intravaginal moisturizer twice a week, with an interval of three days between applications, for a total of 12 weeks. They also received a journal to record adhesion to the treatment and to facilitate the reporting of adverse events.

Before initiating the treatment, patients underwent a gynecological examination (baseline) and then again at the 4th, 8th and 12th weeks of the study. The VHI was the scoring system used to evaluate vaginal elasticity, fluid volume, moisture, pH, and epithelial integrity [12] at baseline as well as at every examination visit following the commencement of the treatment. The first three parameters were graded from 1 (worst condition) to 5 (best condition). The pH scoring was ranked as ≥6.1 (1); between 5.6 and 6.0 (2); between 5.1 and 5.5 (3); between 4.7 and 5.0 (4); and <4.6 (5). The scoring for epithelial integrity included epithelium with petechia (1); bleeding epithelium following light contact (2); bleeding epithelium following scraping; (3); non-friable thin epithelium (4); and normal (5).

In all examination visits the participants answered the Female Sexual Function Index (FSFI questionnaire) [13] in order to evaluate the sexual function. It is a well-established tool that has been validated for the Portuguese language [14] composed of 19 questions covering six domains of female sexual function: desire, arousal, lubrication, orgasm, satisfaction and pain. The summary score ranges from 2 to 36, with low scores indicating severe female sexual dysfunction.

At the end of the study, patients evaluated the non-hormonal intravaginal moisturizer according to four aspects. The first revealed the level of satisfaction with the mooisturizer, according to the following scale: 1 = very satisfied; 2 = satisfied; 3 = indifferent; 4 = dissatisfied; or 5 = very dissatisfied. The second revealed their satisfaction with the product application system (only twice a week), according to the following scale: 1 = very satisfied; 2 = satisfied; 3 = indifferent; 4 = dissatisfied; or 5 = very dissatisfied. The third revealed the sense of the patients' well-being after using the product, including the change in the severity of vaginal dryness, vaginal itching and soreness of the vaginal mucosa. The following scale was used: 1 = very poor; 2 = poor; 3 = unchanged; 4 = good; or 5 = very good. The fourth revealed their perception regarding the discharge of the product (if the product run or was held by the vaginal mucosa) according to the following scale: 1 = high; 2 = medium; 3 = low; or 4 = no discharge. Tolerability and safety were verified through the identification of adverse events.

Statistical analyses

The sample size was calculated based on the differences in the mean increase of the VHI for vaginal moisture, between visits. The mean differences in efficacy between visits were considered to be approximately 1 point on the VHI scale and the standard deviation of differences equal to 2 points. Additionally, with a power of 80% and a significance level of 5%, it was estimated that 35 patients should complete the study. Considering a possible dropout rate of 30%, a total of 46 patients was needed to be included in the study.

Vaginal moisture levels, fluid volume, elasticity, and epithelial integrity evaluated by the VHI as well as the sexual function assessed by the FSFI were compared using the Friedman test (comparing the medians obtained at each examination visit), and the Wilcoxon test (comparing the medians at the initial and at the final visits). The results were considered significant if $p < 0.05$.

Results

A total of 37 postmenopausal women with vaginal dryness, mean age of 56.2 ± 6.1 years and mean body mass index (BMI) of 27.1 ± 5.9 Kg/m^2 completed the study. Eleven women were excluded: nine due to loss of follow-up and two due to inadequate use of the product (Table 1).

Table 1
General Characteristics of postmenopausal women that initiated the use of Non-Hormonal intravaginal moisturizer.

	Patients that completed the study (n = 37)	Excluded (n = 11)
Age (years)	56.2 ± 6.1 (45–75)	56.1 ± 5.7 (45–75)
BMI (Kg/m^2)	27.1 ± 5.9 (21.4–40.9)	26.8 ± 6.6 (23.2–39.2)
Smokers	8.1%	9%

Values are mean ± SD (minimum-maximum).

The VHI results indicated a significant improvement in the vaginal moisture levels, fluid volume and elasticity ($p < 0.0001$) as well as in the vaginal epithelial integrity ($p = 0.003$). These differences were observed after the first month of treatment ($p < 0.05$). No difference was observed in the vaginal pH ($p = 0.207$) (Table 2).

The FSFI data denoted an improvement of female sexual function in the total score and in all six domains ($p < 0.001$) (Table 3). Sexual function improvement was observed after the first month of treatment for the domains arousal, lubrication, orgasm, satisfaction, and pain. After the second month of treatment, improvement was detected for the domain desire ($p < 0.05$).

At the end of the study, 59.5% of patients reported to be very satisfied with the treatment, 37.8% were satisfied, and 2.7% were indifferent. None of the patients reported dissatisfaction or strong dissatisfaction with the treatment. Product application was reported as very satisfactory by 56.8%, satisfactory by 40.5%, and indifferent by 2.7% of the patients. The sense of well-being was considered as very good by 51.4%, good by 40.5%, and unchanged by 8.1% of the patients. Moreover, 91.9% reported that the product did not leak and did not stick to the vaginal mucosa.

The most commonly reported adverse events were mild itching at the beginning of the treatment (15.4%) and mild cramps (17.9%) after the second examination. None of these were characterized as severe and did not last for more than 24 h.

Discussion

Vaginal moisturizers are the first-line treatment for VVA and are primarily intended for the relief of vaginal dryness on a day-to-day basis [7]. However, knowledge about the efficacy and the impact of vaginal moisturizers on sexual function remains poorly known. Our study demonstrates that the use of non-hormonal intravaginal moisturizer (Hidrafemme) for 12 weeks relieves the symptoms associated with vaginal dryness and mitigates sexual dysfunction associated with dyspareunia.

Life expectancy has increased significantly and currently many women will spend one-third of their lives in the hypoestrogenic state of the postmenopausal period [15]. Hypoestrogenism is responsible for several symptoms, including those related to VVA [16]. Although estrogen therapy based on the local or systemic administration are efficient for the treatment of the symptoms associated with VVA in postmenopausal women, they are contra-indicated in some cases such as women with vaginal/uterine bleeding and endometrial or breast cancer. Considering the proportions of this problem, VVA should be getting more attention, especially for women with contraindications and given the dissatisfaction of the patients with the treatments currently employed to alleviate VVA symptoms [5].

The non-hormonal intravaginal moisturizer (Hidrafemme) is a pH-balanced vaginal moisturizer and its formulation retains some of the major components of Replens since the latter is a moisturizing base of polycarbophil carbomer. Following the use of the non-hormonal intravaginal moisturizer, we found a significant improvement in the vaginal moisture levels, fluid volume and elasticity ($p < 0.0001$), as well as in the vaginal epithelial integrity ($p = 0.003$). An open-label study comparing the effects of Replens with a local estrogen therapy (Premarin) revealed the moisturizer as a safe and effective alternative to the estrogen vaginal cream, with patients showing increased vaginal moisture, fluid volume, and elasticity as well as a return of the premenopausal vaginal pH state [17]. A randomized, double-blind placebo-controlled trial of thrice weekly application of a topical vaginal pH-balanced gel versus placebo in 86 breast cancer survivors showed improved vaginal dryness, dyspareunia, and vaginal pH measured by the VHI and a visual analog scale after three months [18]. Although the present study did not intend to compare the effects observed with the non-hormonal intravaginal moisturizer with estrogen-based vaginal therapies or with patients for which the use of such hormonal-based creams is not indicated, we speculate that the non-hormonal intravaginal moisturizer will have similar positive results as demonstrated for Replens in these studies.

Our results are not in agreement with a previous study that noted the lowering of vaginal pH of 70 pregnant women who used the polycarbophil gel (Miphil) [19]. The participants included in the present study already presented vaginal pH within the normal range (pH = 6) and Hidrafemme did not affect this pH ($p = 0.207$). This is a positive factor favoring the use of Hidrafemme, since women are advised to choose products physiologically similar to natural vaginal secretions and with optimally balanced osmolality and pH [20].

Importantly, treatment with the non-hormonal intravaginal moisturizer resulted in clinical improvement of the female sexual function evaluated by the FSFI and reduced pain during sexual intercourse. Many women perceive vaginal dryness and discomfort as having a substantial negative impact on their lives, particularly regarding their sexual intimacy, ability to have a loving relationship, and overall quality of life [21]. The vaginal damage observed in patients with VVA interferes with the typical female sexual response. Vaginal moisturizers re-hydrate the dry mucosa and alter the fluid content of the endothelium by adhering to the vaginal mucosa, thus mimicking natural secretions [20]. Our results with the non-hormonal intravaginal moisturizer (Hidrafemme) indicate that this moisturizer is beneficial to women with symptoms of vaginal dryness and reporting pain during sexual activity since the patients described the improvement in all domains of sexual response evaluated by the FSFI. Improvement of pain in sexual intercourse in postmenopausal women with vaginal dryness was also observed in a study of 45 patients who used a similar intravaginal Moisturizer (Replens) for four weeks [22]. Another study with a polycarbophil-based vaginal moisturizer also described the improvement of the female sexual function when

Table 2
Improvement of Vaginal Health Index of postmenopausal women after treatment with Non-Hormonal Intravaginal Moisturizer.

VHI	Baseline (n = 37)	Post-treatment (n = 37)	p
Vaginal elasticity	2 ± 1 (2–4)	4 ± 1 (3–5)	<0.0001
Fluid volume	2 ± 2 (1–5)	5 ± 0 (4–5)	<0.0001
Vaginal moisture	3 ± 1 (1–5)	5 ± 0 (4–5)	<0.0001
pH	2 ± 2 (1–5)	2 ± 2 (1–4)	0.18
Epithelial integrity	5 ± 1 (4–5)	5 ± 0 (2–5)	0.003

Friedman test.
Values are median ± IQR. (minimum-maximum).

Table 3
Improvement of sexual function of postmenopausal women after treatment with Non-Hormonal Intravaginal Moisturizer.

FSFI domain	Baseline (n = 37)	Post-treatment (n = 37)	p
Total	18.8 ± 6.9 (9.6–30.9)	30.9 ± 8 (1.2–35.4)	<0.0001
Desire	2.4 ± 1.8 (1.2–6)	4.2 ± 1.2 (1.2–6)	<0.0001
Arousal	3 ± 1.2 (1.2–5.1)	4.8 ± 1.3 (0–5.7)	<0.0001
Lubrication	2.6 ± 1.8 (1.2–6)	5.4 ± 1.3 (0–6)	<0.0001
Orgasm	3.2 ± 2.1 (1.2–5.2)	5.4 ± 2.5 (0–6)	<0.0001
Satisfaction	4 ± 1.6 (0–6)	6 ± 1.6 (0–6)	<0.0001
Pain	3.2 ± 2 (0–6)	6 ± 0 (0–6)	<0.0001

Friedman test.
Values are median ± IQR. (minimum-maximum).

compared with a low-dose estrogen therapy [23]. On the other hand, two recent studies from the same group evaluated 302 postmenopausal women that used vaginal estradiol, vaginal moisturizer and placebo and concluded that the estradiol but not the moisturizer, modestly improved sexual function [24] and that neither estradiol nor moisturizer is better than placebo in reducing vulvovaginal symptoms [25].

Acceptability of the product was determined based on patients' subjective evaluation. Most participants (97.3%) were satisfied or very satisfied with the product; 91.9%, indicated that their sense of wellness following the use of the moisturizer was good or very good; Most women (97.3%) also reported to be satisfied or very satisfied with the system of product application (twice-weekly) and 94.6% revealed none or a low discharge of the moisturizer. Finally, we demonstrated that the non-hormonal intravaginal moisturizer (Hidrafemme) is safe and well tolerated, as none of the participants presented sever adverse events.

In conclusion, our study suggests that treatment with the non-hormonal intravaginal moisturizer (Hidrafemme) is a safe and efficient therapeutic option for the improvement of vaginal dryness with encouraging benefits for the sexual function of postmenopausal women. Further controlled, randomized studies are necessary to confirm our results.

Funding

This work was supported by Farmoquimica.

Conflict of interest

All authors report no conflicts of interest, did not receive grants for this study or honorarium as a speaker.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Study was approved by the research ethics committee of the Universidade Federal de Minas Gerais (UFMG) under COEP-1379159.

Author contribution

FV: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration.

CR: Data curation, Methodology, Approval of the final version of the manuscript.

AR: Data curation, Methodology, Approval of the final version of the manuscript.

TB: Data curation, Methodology, Approval of the final version of the manuscript.

SG: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, review & editing.

Acknowledgement

This work was supported by Farmoquimica.

References

[1] Lev-Sagie A. Vulvar and vaginal atrophy: physiology, clinical presentation, and treatment consiederations. Clin Obstet Gynecol 2015;58:476–91.
[2] Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. J Sex Med 2009;6:2133–42.
[3] Nappi RE, Palacios S. Impact of vulvovaginal atrophy on sexual health and quality of life at postmenopause. Climacteric 2014;17:3–9.
[4] Kingsberg SA, Rezaee RL. Hypoactive sexual desire in women. Menopause 2013;20:1284–300.
[5] Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): prevalence and impact on quality of life (QoL). Maturitas 2016;94:87–91.
[6] Nappi RE, de Melo NR, Martino M, Celis-González C, et al. Vaginal health: insights, views & attitudes (VIVA-LATAM): results from a survey in Latin America. Climacteric 2018;21:397–403.
[7] The North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society. Menopause 2013;20:888–902 quiz 903-4.
[8] Rees M, Pérez-López FR, Ceasu I, et al. EMAS clinical guide: low-dose vaginal estrogens for postmenopausal vaginal atrophy. Maturitas 2012;73:171–4.
[9] Sturdee DW, Panay N, International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 2010;13:509–22.
[10] Lubrizol, Bioadhesion, Pharmaceutical Bulletin 23. Edition: May 31, 2011. Previous Editions: August 15, 2005/October 29, 2008.
[11] Frobenius W, Bogdan C. Diagnostic value of vaginal discharge, wet mount and vaginal pH - an update on the basics of gynecologic infectiology. Geburtshilfe Frauenheilkd 2015;75:355–66.
[12] Bachmann GA, Notelovitz M, Kelly SJ, Owens A, Thompson C. Long-term nonhormonal treatment of vaginal dryness. Clin Pract Sex 1992;8:8.
[13] Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther 2005;31:1–20.
[14] Pacagnella Rde C, Vieira EM, Rodrigues Jr OM, Souza C. [Cross-cultural adaptation of the female sexual function index]. Cad Saude Publica 2008;24:416–26.
[15] Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. Maturitas 2010;67:233–8.
[16] Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. Mayo Clin Proc 2010;85:87–94.
[17] Nachtigall LE. Comparative study: replens versus local estrogen in menopausal women. Fertil Steril 1994;61:178–80.
[18] Lee YK, Chung HH, Kim JW, Park NH, Song YS, Kang SB. Vaginal pH-balanced gel for the control of atrophic vaginitis among breast cancer survivors: a randomized controlled trial. Obstet Gynecol 2011;117:922–7.
[19] Paternoster DM, Tudor L, Milani M, Maggino T, Ambrosini A. Efficacy of an acidic vaginal gel on vaginal pH and interleukin-6 levels in low-risk pregnant women: a double-blind, randomized placebo-controlled trial. J Matern Fetal Neonatal Med 2004;15:198–201.
[20] Edwards D, Panay N. Treating vulvovaginal atrophy/genitourinary syndrome of menopause: how important is vaginal lubricant and moisturizer composition? Climacteric 2016;19:151–61.
[21] Simon JA, Kokot-Kierepa M, Goldstein J, Nappi RE. Vaginal health in the United States: results from the vaginal health: insights, views & attitudes survey. Menopause 2013;20:1043–8.
[22] Loprinzi CL, Abu-Ghazaleh S, Sloan JA, et al. Phase III randomized double-blind study to evaluate the efficacy of a polycarbophil-based vaginal moisturizer in women with breast cancer. J Clin Oncol 1997;15:969–73.
[23] Biglia N, Peano E, Sgandurra P, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrinol 2010;26:404–12.
[24] Diem SJ, Guthrie KA, Mitchell CM, et al. Effects of vaginal estradiol tablets and moisturizer on menopause-specific quality of life and mood in healthy postmenopausal women with vaginal symptoms: a randomized clinical trial. Menopause 2018;25:1086–93.
[25] Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs placebo for treating postmenopausal vulvovaginal symptoms: a randomized clinical trial. JAMA Intern Med 2018;178:681–90.