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Women's Health, Issues and Care

Research Article

Effective treatment of vulvar -vaginal atrophy with a new medical device in gel: A Pilot study

Filippo Murina*, Franco Vicariotto, Stefania Di Francesco and Silvia Oneda

Lower Genital Tract Disease Unit, V. Buzzi Hospital–University of Milan, Milan, Italy

Abstract

Objective: To assess efficacy and tolerability of a of a new medical device in gel based on the synergic combination of Nioskin™ Red Clover Extract noisome (NRC) and SylTech™ system (SB), a complex of silicium microcrystals covalently bound with silver ions associated with hyaluronic acid to the treatment of vaginal atrophy in postmenopausal women.

Methods: Fifty five women were treated for 12 weeks with NRC+SB vaginal gel (0.75 g/day) for 12 weeks. After therapy, the vaginal atrophy symptoms (dyspareunia, dryness and burning) were evaluated through a 10-cm VAS. Visual examination of the vagina and vulvar vestibule was also conducted, which included observations for petechiae, pallor, friability, dryness, and redness in the mucosa. Ratings were based on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). The endometrial safety (by transvaginal ultrasonography) was also evaluated through at screening and the end of the trial.

Results: NRC+SB vaginal gel appears to be effective for relief symptoms related to vaginal atrophy and an improvement of vaginal and vestibular trophism was noted. No changes in endometrial thickness were observed at study endpoint.

Conclusion: NRC+SB vaginal gel proved good treatment options for relief of vulvovaginal symptoms particularly in women who do not wish to use hormonal therapy or have contraindications for this treatment.

Introduction

Genitourinary syndrome of menopause (GSM) is chronic, progressive vulvovaginal, sexual, and lower urinary tract condition characterized by related estrogen deficiency involving changes to the vulva, vagina, urethra, and bladder. Symptoms may include genital dryness, burning, and irritation; sexual symptoms of diminished lubrication and pain; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections [1].

Unlike the vasomotor symptoms that typically accompany menopause, GSM symptoms do not diminish over time and are unlikely to resolve without treatment [2]. The symptoms and consequences of GSM can cause years of vulvovaginal discomfort, having a significant impact on quality of life for women in the postmenopausal stage of life.

Despite its high incidence, urogenital atrophy is an underreported and underdiagnosed condition.

In fact, few women seek medical attention for vulvovaginal symptoms, often because they are uncomfortable talking about such a personal issue. According to The North American Menopause Society (NAMS), an estimated about 40% of postmenopausal women experience symptoms related to urogenital atrophy but this aspect of menopause is often overlooked and undermanaged [1].

Only 20–25% of symptomatic women seek medical help, despite the availability of safe and effective options to treat vaginal and urological symptoms related to estrogen deficiency [3].

Because women have a higher life expectancy than men, and approximately more than 17% of the population will be over the age of 65 by 2030, the consequences of declined endogenous estrogen levels in menopausal women should be of great interest to clinicians [4].

For symptomatic VVA that does not respond to the patient's satisfaction with nonhormonal interventions, low-dose vaginal ET is likely to provide greater benefit. For decades, systemic and vaginal estrogen has been the gold standard for treatment of symptomatic VVA [5]. Estrogen delivered locally is now the preferred mode of delivery when vaginal symptoms are the only complaint. Low-dose vaginal ET can provide sufficient estrogen to relieve symptoms with minimal systemic absorption. Vaginal ET has been shown to be more effective than systemic oral ET in the relief of VVA symptoms, with 80% to 90% of women reporting a favorable response compared with 75% of women using oral ET.64,65 Studies of the effectiveness of vaginal ET have used subjective and objective outcome measures, including improvements in atrophic symptoms (including dyspareunia when that indication was sought), lower urinary tract symptoms, gross vaginal mucosal appearance, decreases in vaginal pH [6].

Hormonal replacement therapy (HRT), via systemic or topical routes, is widely used for the treatment of menopausal effects on urogenital tract. All local vaginal estrogen products have been

***Corresponding author:** Filippo Murina, Lower Genital Tract Disease Unit, V. Buzzi Hospital–University of Milan, Milan, Italy, Tel: +39 02 503111; E-mail: filippomurina@tin.it

Received: December 01, 2017; **Accepted:** December 28, 2017; **Published:** December 30, 2017

recognized as being effective and well tolerated for treating vaginal atrophy. In recent years, phytoestrogen supplements have become attractive as safer alternatives, and their efficacy has been investigated in experimental and clinical trials [7]. Only two studies have explored the potential benefits of isoflavones for the treatment of postmenopausal vaginal dryness. In one double-blind, crossover RCT, 102 the isoflavone treatment consisted of 114 mg isoflavones/day for 3 months.

The investigators concluded that the isoflavones had no effect on subjective perception of vaginal dryness or on objective findings in the vagina. A year later, in a second crossover RCT, the peri- and postmenopausal women were given either a daily placebo or 25 g soy. The authors concluded that a soy-rich diet did not relieve urogenital symptoms, restore vaginal epithelium, or improve vaginal health [8,9]. The phytoestrogens identified in red clover are isoflavones (formononetin, biochanin A, diadzen and genistein) which are able to act as selective oestrogen receptor modulators [10]. The aim of the current investigation was to evaluate the efficacy of a new medical device in gel based on the synergic combination of Nioskin™ Red Clover Extract noisome (NRC), a unique ultra-deformable vesicles effectively delivering the concentrated isoflavones aglycones of Red Clover, and SylTech™ system (SB), a complex of silicium microcrystals covalently bound with silver ions associated with hyaluronic acid, in the supportive treatment of GSM related symptoms.

Methods

Patients: The inclusion criteria were: non-hysterectomized, postmenopausal (1 or more years since final menstrual cycle) women who were 45 years of age or older with symptoms of vaginal dryness, vulvar or vaginal burning or pain, and dyspareunia. All participants were required to have an endometrial thickness of less than 4.0 mm as assessed by transvaginal ultrasonography, and a normal mammography during the 6 months leading up to study entry.

Exclusion criteria were: use of any investigational drug or exogenous sex hormones within the 3 months leading up to study drug initiation, or current use of corticosteroids, known or suspected history of hormone-dependent tumor, breast carcinoma, genital bleeding of unknown cause, acute thromboembolic disorder associated with estrogen use, vaginal infection requiring treatment, allergy to the test drug or its constituents, hot flashes, and any serious disease or chronic condition that could interfere with study compliance.

Study design: This observational clinical study was performed in accordance with the Declaration of Helsinki and International Standards of Good Clinical Practice (ICH-E6). The study protocol and patient informed consent form were approved by the local Ethics Committee. At the first visit, written informed consent was obtained and inclusion and exclusion criteria assessed.

Eligible participants received a 1mg gel containing NRC and SB. Patients were instructed to apply gel internally in vagina and on the vulvar vestibule daily for 12 weeks (0.75g), before going to sleep.

Assessments: All women underwent medical examination (interview, gynecologic examination, mammography and transvaginal ultrasonography) in order to determine patient eligibility.

During the visits at 12 weeks, patients reported by a questionnaire any symptoms of vaginal dryness, vulvar or vaginal burning and/or pain and dyspareunia. Participants reported intensity of GSM symptoms using a 10-cm VAS. The scale's left extremity indicates the complete absence of symptoms (0) and the right extremity indicates the worst possible symptom, and women rated dyspareunia, dryness, or burning from 0 to 10. Visual examination of the vagina and vulvar vestibule was also conducted, which included observations for petechiae, pallor, friability, dryness, and redness in the mucosa. Ratings were based on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Statistical analyses (Wilcoxon Mann–Whitney test- Kruskal–Wallis test) were performed by comparing endometrial thickness and changes in scores between baseline and weeks 4 and 12 for each symptom and sign. Data were expressed as means and 95% confidence intervals (CIs), accompany P values for all the endpoints.

Results

Of the 55 women enrolled in the study, 52 (94,5 %) completed the 12 weeks treatment. Only one case of drop out with interruption for burning was observed and about 10% of subjects reported an initial light burning at application, symptom that disappears with the treatment naturally.

Patient baseline characteristics are shown in Table 1.

After 12 weeks of therapy with gel containing NRC and SB , there was a statistically significant decrease from baseline in the mean score of the dyspareunia , vulvar/vaginal burning or pain and vaginal dryness (Figure 1 and 2).

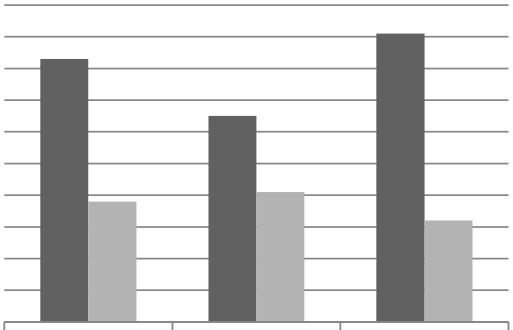
Statistically significant improvement of vestibular and vaginal trophism were also found after the 12 weeks of therapy (Fig. 2). Analysis of endometrial echo before and after 12 weeks' treatment revealed no statistically significant difference (p = 0.652). Endometrial thickness was <4 mm in all cases.

Discussion

Our results suggest that a 12-week treatment using a NRC+SB vaginal gel led to improvements in vulvo-vaginal atrophy symptoms and to a significant increase vaginal and vestibular trophism. Currently, an effective option for treating vaginal symptoms secondary to hypoestrogenism is natural estrogens [11]. Low-dose vaginal estrogen preparations are effective and generally safe treatments for VVA32, 65 and include creams, tablets, and rings containing estradiol or CEE, available at doses

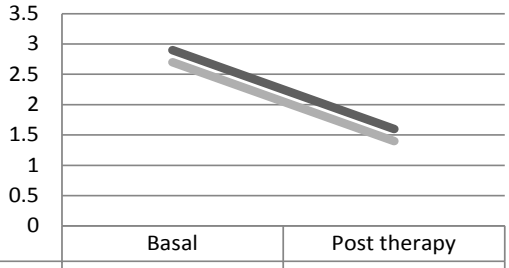
Table 1. Patients Demographics and Baseline Characteristics. Data are presented as the mean values ± standard deviation. *Scored from 0 to 3 (0, none; 1, mild; 2, moderate; 3, severe).

	Patients (n= 55)
Age (y) Range	56.4 (± 5.6) 49-69
Time since last menses (y) Range	8.2 (± 5.3) 1-23
Symptoms (VAS) and Signs*	
Dyspareunia Vulvar/vaginal burning or pain Vaginal dryness Vestibular trophism* Vaginal trophism*	8.3 (± 6.3) 6.5 (± 4.2) 9.1 (±6.9) 2.91 (± 0.30) 2.73 (± 0.38)
Endometrial thickness (mm)	3 (1–4)



	Dyspareunia	Vulvar/vaginal burning or pain	Vaginal dryness
Basal	8.3	6.5	9.1
Post therapy	3.8	4.1	3.2

Figure 1. Symptoms after 12 weeks of therapy. Data of VAS presented as the mean ($p<0.003$).



	Basal	Post therapy
Vestibular trophism	2.9	1.6
Vaginal trophism	2.7	1.4

Figure 2. Vestibular and vaginal trophic score score at baseline and week 12. Data are expressed as score: no atrophy=0, mild=1, moderate=2 and severe=3. Data are expressed as score: no atrophy=0, mild=1, moderate=2 and severe=3.

that result in minimal systemic absorption [12]. A meta-analysis of randomized placebo-controlled studies found that estrogen therapy, in general, relieved vaginal symptoms, and the vaginal therapy was more efficacious than systemic oral therapy [13]. Some studies have shown that vaginally administered estrogens can cause systemic absorption according to type and dose used Nevertheless, this effect represents cause for concern among women with antecedents of breast cancer and other hormone-dependent cancers, or who do not want to use hormone therapy because the fear of a breast cancer onset [14].

Based on the assessment of treatment and symptom severity in this study, NRC+SB vaginal gel was shown to be effective for relieving both moderate and intense symptoms, particularly vaginal dryness complaints and dyspareunia, mirroring the effects of estrogen use. More specifically, post-treatment improvement in vaginal dryness symptoms was seen in 76.7% of women, and dyspareunia complaints, improvements occurred in 66.7% of patients.

Several systematic reviews and meta-analyses have been conducted on clinical trials using red clover for the reduction of vulvo-vaginal menopausal symptoms. Overall, these studies suggest a very small positive effect with uncertain clinical relevance [15,16]. A strength of our therapy was related to the use of a new medical device in gel based on Nioskin™ Red Clover Extract noisome (NRC). This is a unique ultra-deformable vesicle effectively delivering the concentrated isoflavones aglycones of Red Clover allowing to obtain an elevated bioavailability of the drug. Another strength of the trial is the synergic combination SylTech™ system (SB), a complex of silicium microcrystals covalently bound with silver ions associated with hyaluronic acid. SiltechTM microcrystals, the micro-technology ensures a range of particles size averaging of 0.2 - 0.3 micron, achieve the maximum extent of interaction on tissue creating a protective film layer [17]. The effective film barrier assists the natural repair of the tissue creating a microenvironment suitable for a re-epithelization promoted by NRC. It is known that vaginal hormone therapy with conjugated equine estrogen cream can be accompanied by episodes of vaginal bleeding and endometrial thickening. In our study however, no genital bleeding was reported while ultrasonography findings disclosed no increase in endometrial echo. The very low rate of discontinuation shows high tolerability of the vaginal gel. In fact, vestibular mucosa is very reactive and therefore more vulnerable to the effects of externally applied agents. In this study, the highly hydrating properties of the gel were possibly adequate for preventing vestibular discomfort.

One limitation of this study is the absence of follow-up, but the therapy may be continued for as long as the patients are distressed by their symptoms without estrogen intervention.

In conclusion, NRC+SB vaginal gel proved good treatment options for relief of vulvovaginal symptoms particularly in women who do not wish to use hormonal therapy or have contraindications for this treatment.

References

1. Portman DJ, Gass MLS (2014) Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. Maturitas 79: 349-354.

2. Gandhi J, Chen A, Dagur G, et al. (2016) Genitourinary syndrome of menopause: An overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. Am J Obstet Gynecol 215: 704–711.

3. Nappi RE, Kokot-Kierepa M (2012) Vaginal Health: Insights, views and attitudes (VIVA): Results from an international survey. Climacteric 15: 36–44.

4. Sturdee DW, Panay N (2010) On behalf of the International Menopause Society Writing Group. Recommendations for the management of postmenopausal vaginal atrophy. Climacteric 13: 509-522.

5. [No authors listed] (2013) Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society Menopause. Menopause 20: 888-902

6. Archer DF (2010) Efficacy and tolerability of local estrogen therapy for urogenital atrophy. *Menopause* 17: 194-203. [Pubmed]

7. Moraes ARB (2009) The effects of topical isoflavones on postmenopausal skin: doubleblind and randomized clinical trial of efficacy. European Journal of Obstetrics, Gynecology, and Reproductive Biology 146: 188-192.

8. Nikander E, Rutanen EM, Nieminen P, et al. (2005) Lack of effect of isoflavonoids on the vagina and endometrium in postmenopausal women. Fertil Steril 83: 137-142.

9. Ishiwata N, Melby MK, Mizuno S, et al. (2009) New equol supplement for relieving menopausal symptoms: randomized, placebo-controlled trial of Japanese women. Menopause 16: 141-148.

10. Beck V, Rohr U, Jungbauer A, et al. (2005) Phytoestrogens derived from red clover: an alternative to estrogen replacement therapy? J Steroid Biochem Mol Biol 94: 499–518.

11. Rees M, Pérez-López FR, Ceasu, et al. (2012) EMAS clinical guide: Low-dose vaginal estrogens for postmenopausal vaginal atrophy. Maturitas 73: 171-174.

12. Santen RJ (2015) Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. Climacteric 18: 121-134.

13. Pinkerton JV, Sánchez Aguirre F, Blake J, et al. (2017) The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 24: 728-753.

14. Suckling JA, Kennedy R, Lethaby A, et al. (2006) Local oestrogen therapy for vaginal atrophy in post menopausal women. Cochrane Database of Systematic Reviews 4: CD001500.

15. Chen MN, Lin CC, Liu CF (2015) Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric 18: 260-269. [Pubmed]

16. Ghazanfarpour M. , Sadeghi R. , Roudsari RL, et al. (2015) Red clover for treatment of hot flashes and menopausal symp- toms: a systematic review and meta-analysis. J. Obstetrics Gynaecol pp. 1–11.

17. SiltehTM Micro Silver Micro System. www.linnea.ch.