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ABSTRACT

In a single arm pilot study, 47 post-menopausal women affected by vulvovaginal atrophy (VVA) were enrolled. All women underwent vaginal health index score (VHIS) evaluation and completed the female sexual function index (FSFI) questionnaire at baseline evaluation (T0) and following 15 days of vaginal cream treatment with one application per day (T1). Following treatment there was a significant improvement of all VHIS parameters and total score ($p<0.0001$). Similarly, there was a significant improvement of 4 FSFI domains (lubrication, orgasm, satisfaction and pain) and total score ($p=0.001$). None of the patients reported any local or systemic side effect during the treatment.

Keywords: Visnadine; Prenylflavonoids; Bovine colostrum; Vulvovaginal atrophy; Menopause; Sexual wellbeing.

Commented [AL1]: We used the term “single arm pilot study” both in the title of the study and the body of the text, as suggested by Reviewer 2.

Introduction

Accumulating evidence suggests that vulvovaginal atrophy (VVA) is strongly associated with female sexual dysfunction (FSD) among sexually active postmenopausal women [1, 2].

Visnadine, an active ingredient of the fruit of *Ammi visnaga,* showed powerful vasodilatory activity due to the inhibitory effects on voltage-gated L-type Ca^{2+} channels, and has been found to ameliorate female sexual arousal disorder [3]. Furthermore, prenylflavonoids and phytoestrogens play a potent role as estrogen receptor (ER)-alpha selective agonist [4], thus they may counteract the effects of postmenopausal estrogen loss. Finally, a vaginal cream containing bovine colostrum has been shown to be effective in relieving vaginal dryness and other VVA symptoms in postmenopausal women, after 8 weeks of treatment [5].

Based on this information, we aimed to assess the safety and efficacy of a new vaginal cream containing visnadine, prenylflavonoids and bovine colostrum on Vaginal Health Index Score (VHIS) and Female Sexual Function Index (FSFI) in a cohort of postmenopausal sexually active women affected by VVA.

Methods

A prospective single arm pilot study (ClinicalTrials.gov ID: NCT03281655) was undertaken after institutional review board (IRB) approval, between December 2016 and May 2017 at the Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood “G. Barresi”, University of Messina (Messina, Italy). We consecutively enrolled post-menopausal women affected by VVA, excluding patients affected by relevant comorbidities (chronic cardiovascular, immune, endocrine and metabolic diseases and cancers), smokers and who used any other kind of pharmacologic treatment (including the

substances tested in this study) in the previous 3 months. VVA was defined as self-reporting at least one of the following in the past 4 weeks: vaginal dryness, vaginal itching, vaginal irritation, pain on urination, vaginal pain associated with sexual activity, or vaginal bleeding associated with sexual activity. The inclusion criteria did not have a minimum severity requirement for VVA symptoms.

After informed consent, we recorded age, age of menopause onset, parity and body mass index (BMI) for all enrolled patients. All patients underwent VHIS evaluation, performed always by the same gynecologist in order to avoid inter-observer variability, and filled the FSFI questionnaire. Following baseline evaluation (T0), all the enrolled women underwent 15 days of vaginal treatment with one application (approximately 2 ml) per day of the new vaginal cream (Refeel, I.D.I. Pharma, Italy) containing visnadine (0.30%), prenylflavonoids (0.10%) and bovine colostrum (1%). The total volume of the cream administered during the treatment was 30 ml. The pH of the cream was 5.5. The cream was administered through single-use vaginal dispensers/applicators in the morning, after intimate cleansing. Any patient taking less than 80% of the allocated dose of study drug was regarded as noncompliant and excluded from the study. The study drug was offered for free and none of the enrolled patients were paid to enter or continue the study. Following treatment (T1), all patients were evaluated using VHIS and FSFI, all side effects recorded and an independent data safety and monitoring committee evaluated the results of the study.

Results

A total of 54 women who met the inclusion/exclusion criteria and signed informed consent were enrolled into the study. Since 3 patients discontinued the intervention and 4 were lost to follow-up, the analysis was limited to 47 women. All of them declared that they took at least 90% of the allocated dose of study drug. Mean age was 56.5 ± 4.3 years, mean age at

menopause was 49.7 ± 1.8 years, mean BMI was 27.8 ± 1.7, mean parity was 1.7 ± 0.9.

Following treatment there was a significant improvement of all VHIS parameters (Table 1) including, elasticity, fluid volume and consistency, pH, epithelial integrity and moisture, as well as VHIS total score ($p<0.0001$).

Pre- and post-treatment analyses of FSFI domains showed a significant improvement (Table 1) of 4 FSFI domains (lubrication, orgasm, satisfaction and pain), whereas no statistical differences were noted for the remaining 2 domains (desire, arousal) ($p=0.31$ and $p=0.036$, respectively). In addition, the FSFI total score significantly increased ($p=0.001$) between pre-treatment (22.8 ± 4.2) and post-treatment (25.2 ± 2.4) phases. None of the subjects reported any local or systemic side effect whiles on the treatment.

Discussion

Postmenopause is characterized by several hormonal and metabolic changes, which frequently compromise the quality of life of women. In particular, a number of menopause-related symptoms and signs are derived as a result of severe lack of estrogen production [1, 2].

Based on this information, we tested a new vaginal cream containing visnadine (0.30%), prenylflavonoids (0.10%) and bovine colostrum (1%) in a cohort of sexually active postmenopausal women affected by VVA. According to our preliminary data analysis, the vaginal cream was able to ameliorate both vaginal health and sexual quality, as documented by the significant increase of VHIS and FSFI parameters. Importantly, an excellent safety profile (no side effects during the study period) was noted.

To the best of our knowledge, this is the first single arm pilot study determining the effects of a mixture of visnadine, prenylfavanoids and bovine colostrum for the treatment of postmenopausal VVA. Nevertheless, several limitations of the study should be taken into

account during interpretation of our preliminary data: first of all, the sample size is limited as well as the follow-up, which do not allow to define whether the treatment's effects will last for a longer period; second, it is not possible to ascertain the weight of each component of the cream in improving VVA and sexual wellbeing; third, the study design does not have a control arm allocated with placebo or no-treatment; fourth, we excluded 3 patients who discontinued the intervention, possibly enhancing the treatment effects. Despite these limitations, our preliminary data shows a potential beneficial effect of the new cream in regards to VHIS and FSFI in postmenopausal women with VVA. Since the limitations of this single arm pilot study, the new vaginal cream should be tested in a randomised controlled trial using a placebo cream without the active ingredients or current standard of care treatment.

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