Maturitas 109 (2018) 78–80

Contents lists available at ScienceDirect

Maturitas

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

Preliminary results of a single-arm pilot study to assess the safety and efficacy of visnadine, prenylflavonoids and bovine colostrum in postmenopausal sexually active women affected by vulvovaginal atrophy

Antonio Simone Laganà[a,*], Salvatore Giovanni Vitale[a], Lily Stojanovska[b], Irene Lambrinoudaki[c], Vasso Apostolopoulos[b], Benito Chiofalo[a], Laura Rizzo[a], Francesca Basile[a]

[a] Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy
[b] Centre for Chronic Disease, College of Health and Biomedicine, Victoria University, Melbourne, VIC, Australia
[c] Second Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Greece

ARTICLE INFO

Keywords:
Visnadine
Prenylflavonoids
Bovine colostrum
Vulvovaginal atrophy
Menopause
Sexual wellbeing

ABSTRACT

This single-arm pilot study enrolled 47 post-menopausal women affected by vulvovaginal atrophy (VVA). The Vaginal Health Index Score (VHIS) was evaluated for all women and all completed the Female Sexual Function Index (FSFI) questionnaire at baseline (T0) and after 15 days of vaginal cream treatment with one application per day (T1). Following treatment there was a significant improvement in all VHIS parameters and total score ($p < 0.0001$). Similarly, there was a significant improvement on four FSFI domains (lubrication, orgasm, satisfaction and pain) and total score ($p = 0.001$). None of the patients reported any local or systemic side-effects during treatment.

1. 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,* shows 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] and so 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, using the Vaginal Health Index Score (VHIS) and Female Sexual Function Index (FSFI) in a cohort of postmenopausal sexually active women affected by VVA.

2. 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 postmenopausal women affected by VVA, but excluded patients affected by relevant comorbidities (chronic cardiovascular, immune, endocrine and metabolic diseases and cancers), smokers and who had used any other kind of pharmacological treatment (including the substances tested in this study) in the previous 3 months. VVA was defined as self-reporting of 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 had been given by patients, we recorded their age, age of menopause onset, parity and body mass index (BMI). All patients underwent VHIS evaluation, performed always by the same gynaecologist in order to avoid inter-observer variability, and filled the

* Corresponding author at: Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Via C. Valeria 1, 98125 Messina, Italy.
E-mail address: antlagana@unime.it (A.S. Laganà).

https://doi.org/10.1016/j.maturitas.2017.12.015
Received 24 August 2017; Received in revised form 20 December 2017; Accepted 22 December 2017

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 non-compliant and excluded from the study. The study drug was offered for free and none of the enrolled patients was paid to enter or continue the study. Following treatment (T1), all patients were evaluated using VHIS and FSFI, all side-effects were recorded and an independent data safety and monitoring committee evaluated the results of the study.

3. Results

A total of 54 women who met the inclusion/exclusion criteria and gave written 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 showed a significant improvement (Table 1) on 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-effects while on treatment.

4. Discussion

Postmenopause is characterised by several hormonal and metabolic changes, which frequently compromise quality of life. In particular, a number of menopause-related symptoms and signs result from the 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 in the interpretation of our preliminary data: first of all, the sample size is limited, as well as the follow-up, and we were unable to determine whether the treatment's effects will last for longer than the 15-day study period; second, it was not possible to ascertain the contribution of each component of the cream to the improvement in VVA and sexual wellbeing; third, the study design does not have a control arm (placebo or no treatment); fourth, we excluded 3 patients who discontinued the intervention, and this might have enhanced the treatment effects. Despite these limitations, our preliminary data show a potential beneficial effect of the new cream with regard to VHIS and FSFI in postmenopausal women with VVA. Given 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.

Contributors

Antonio Simone Laganà conceived and designed the experiments.
Salvatore Giovanni Vitale drafted the paper.
Lily Stojanovska analysed and interpreted the data.
Irene Lambrinoudaki analysed and interpreted the data.
Vasso Apostolopoulos drafted the paper.
Benito Chiofalo contributed to the data collection and analysis.
Laura Rizzo performed the experiments.
Francesca Basile performed the experiments.
All authors contributed to the drafting and revision of the manuscript, and saw and approved the final manuscript.

Conflict of interest

The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company.

Table 1
Analysis of Vaginal Health Index and Female Sexual Function Index between pre- and post-treatment phases.

Vaginal Health Index parameters	Pre-treatment	Post-treatment	p
Elasticity	1.9 ± 0.6 (1.73–2.07)	2.3 ± 1.0 (2.01–2.59)	0.02
Fluid volume and consistency	2.1 ± 0.6 (1.93–2.27)	2.5 ± 1.0 (2.21–2.79)	0.02
pH	2.4 ± 0.9 (2.14–2.66)	2.9 ± 1.1 (2.59–3.21)	0.02
Epithelial integrity	2.7 ± 1.1 (2.39–3.01)	3.3 ± 1.2 (2.96–3.64)	0.01
Moisture	2.2 ± 0.7 (2.00–2.40)	2.7 ± 1.0 (2.41–2.99)	0.006
Total	11.3 ± 2 (10.73–11.87)	13.8 ± 2.1 (13.20–14.40)	< 0.0001

Female Sexual Function Index parameters	Pre-treatment	Post-treatment	p
Desire	3.4 ± 1.0 (3.11–3.69)	3.6 ± 0.9 (3.34–3.86)	0.31
Arousal	3.9 ± 1.0 (3.61–4.49)	4.1 ± 1.1 (3.79–4.41)	0.36
Lubrication	3.4 ± 0.7 (3.20–3.60)	4.0 ± 1.0 (3.71–4.29)	0.001
Orgasm	4.1 ± 1.0 (3.81–4.39)	4.6 ± 0.7 (4.40–4.80)	0.006
Satisfaction	4.3 ± 0.9 (4.04–4.56)	4.7 ± 0.4 (4.59–4.81)	0.006
Pain	3.7 ± 0.9 (3.44–3.96)	4.3 ± 1.1 (3.99–4.61)	0.005
Total	22.8 ± 4.2 (21.60–24.00)	25.2 ± 2.4 (24.51–25.89)	0.001

Data are expressed as means ± standard deviation, with confidence interval at 95%.

Funding

No specific grant was received for this research.

Ethical approval

All procedures performed in this study 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. Informed consent was obtained from all individual participants included in the study.

Provenance and peer review

Peer review was directed by Professor Margaret Rees independently of Irene Lambrinoudaki (one of the authors and an Editor of *Maturitas*), who was blinded to the process.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Acknowledgments

The authors acknowledge the Junior Mentorship Program of the European Menopause and Andropause Society.

References

[1] R. Hayes, L. Dennerstein, The impact of aging on sexual function and sexual dysfunction in women: a review of population-based studies, J. Sex. Med. 2 (2005) 317–330.

[2] K.B. Levine, R.E. Williams, K.E. Hartmann, Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women, Menopause 15 (2008) 661–666.

[3] S. Caruso, D. Mauro, M. Cariola, V. Fava, A.M.C. Rapisarda, A. Cianci, Randomized crossover study investigating daily versus on-demand vulvar Visnadine spray in women affected by female sexual arousal disorder, Gynecol. Endocrinol. (2017), http://dx.doi.org/10.1080/09513590.2017.1354366.

[4] O. Schaefer, M. Hümpel, K.H. Fritzemeier, R. Bohlmann, W.D. Schleuning, 8-Prenyl naringenin is a potent ERalpha selective phytoestrogen present in hops and beer, J. Steroid. Biochem. Mol. Biol. 2–3 (2003) 359–360.

[5] R.E. Nappi, A. Cagnacci, A.M. Becorpi, C. Nappi, A.M. Paoletti, M. Busacca, S. Martella, M. Bellafronte, Z. Tredici, C. Di Carlo, V. Corda, M. Vignali, M. Bagolan, M. Sardina, Monurelle Biogel® vaginal gel in the treatment of vaginal dryness in postmenopausal women, Climacteric 20 (2017) 467–475.