Randomized crossover study investigating daily versus on-demand vulvar Visnadine spray in women affected by female sexual arousal disorder

Salvatore Caruso, Diletta Mauro, Maria Cariola, Valentina Fava, Agnese Maria Chiara Rapisarda & Antonio Cianci

To cite this article: Salvatore Caruso, Diletta Mauro, Maria Cariola, Valentina Fava, Agnese Maria Chiara Rapisarda & Antonio Cianci (2017): Randomized crossover study investigating daily versus on-demand vulvar Visnadine spray in women affected by female sexual arousal disorder, Gynecological Endocrinology, DOI: 10.1080/09513590.2017.1354366

To link to this article: http://dx.doi.org/10.1080/09513590.2017.1354366

Published online: 27 Jul 2017.
ABSTRACT
The aim of the study was to verify the efficacy of vulvar Visnadine spray in premenopausal women affected by female sexual arousal disorder (FSAD). Thirty-eight women aged 25–40 years affected by FSAD were enrolled in the randomized crossover study, by two possible sequences: on-demand, washout, daily (A sequence); and daily, washout, on-demand (B sequence). The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS) were used to assess sexual function and sexual distress, respectively. Color Doppler ultrasonography was used to measure clitoral blood flow. The study had two follow-ups at 30 (T1) and 60 days (T2). Thirty-one women completed the study. Mean (SD) sexual activity and vulvar Visnadine spray usage was 1±0.9 weekly during on-demand administration for both the sequences (Vs T0, p=NS). The mean sexual activity during daily usage was 2±0.9 (Vs T0, p<.004) and 2±0.8 (Vs T0, p<.001) for A and B sequences, respectively. FSFI total score, particularly genital arousal, improved more during the daily than during on-demand phases of both sequences (p<.001). Finally, clitoral blood flow improved significantly during daily usage of both the sequences (p<.001). Our study suggests that vulvar Visnadine spray could improve sexual performance of women affected by FSAD, producing changes in subjective and objective sexual aspects.

INTRODUCTION
Female sexual disorder (FSD) is a highly prevalent problem found in different age groups [1,2], and female sexual arousal disorder (FSAD) consists in the persistent or recurrent inability to attain or to maintain until completion of sexual activity, an adequate lubrication-swelling response of sexual excitement. Moreover, the disorder has to cause marked distress or interpersonal difficulty, not due exclusively to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medication [3,4]. It has become increasingly evident that FSDs can occur secondary to medical problems and have an organic basis [5].

The female genital sexual response is mediated via the release of neurotransmitters causing relaxation of vascular and non-vascular smooth tissue, increased pelvic blood flow, vaginal lubrication, and clitoral and labial engorgement, involving the nitric oxide-cGMP pathway [6].

Currently, there are potential therapeutic options for the treatment of FSDs and these options include both hormonal and pharmacological therapies [7,8]. Pharmacologic treatments may be optional for treating physiologic needs, imbalances, or symptomatic complaints, and comprise only one part of the overall management of women with FSDs [9].

Visnadine is an active principle of the fruit of Ammi visnaga, a plant traditionally used in cardiovascular disorders, having peripheral and coronary vasodilator activities, mainly used for the treatment of angina pectoris [10]. Visnadine acts by inhibiting the contractile responses mediated by Ca²⁺ entry through L-type Ca²⁺ channels [11,12].

The objective of this study was to evaluate the effect of vulvar Visnadine spray (Refeel® Spray, IDI Pharma, Italy) on the external genitalia of women with FSAD.

MATERIALS AND METHODS
A prospective, randomized, crossover study was performed at the Family Planning Centre of the Research Group for Sexology of the Department of General Surgery and Medical Surgical Specialties, School of Medicine, University of Catania, Italy. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration.

Fifty-two consecutive volunteer premenopausal women affected by FSAD, having regular menstrual cycle with ovulation, were invited to participate. Particularly, women requesting consultation for lack of vaginal lubrication or for being slow to respond after sufficient sexual stimulation with a recurrent inability to attain or maintain sufficient sexual excitement on the basis of the DSM-IV FSAD definition, were included in the study [13]. These women were highly sexually aroused in their minds but were not genitally responsive, this included lubrication and sexual pleasure after genital stimulation.

All the women gave their written informed consent before entering the study. The study was not advertised and no remuneration was offered.
The sample consisted of women having a stable, satisfying heterosexual relationship for at least 6 months, and subjectively normal sexual desire toward their partners. Women with a history of hypertension, coronary artery disease, thromboembolic disorder, hepatic and/or renal disease, diabetes or neoplasia; who were taking hormone therapy or oral contraceptives; who had a history of smoking or alcohol abuse; without a sexual partner, or were affected by situational sexual dysfunction with their partner, or had a partner with sexual dysfunction; and/or with dysphoric arousal and/or sensation of unpleasant genital engorgement; or reporting to be affected by depression and/or using antidepressant drugs and/or undergoing psychological counseling for depressive symptoms, were excluded from the study.

**Procedures**

During enrollment, all inclusion and exclusion criteria were adopted. Women underwent a physical examination, including assessment of vital signs, and an electrocardiogram. In addition, blood samples were obtained from all participants to measure Testosterone [(TT, ng/dL), normal range 0.3–1.2 ng/mL], SHBG (nmol/L) and Prolactin [(PRL, ng/mL), normal range 5–25 ng/mL], measured by enzyme-linked immunosorbent assay (ELISA, Elecsys Systems 2010, Roche, Monza, Italy). The free androgen index (FAI) was calculated by using FAI = [TT/SHBG (nmol/L)]/C2 × 100.

A Sexual History Interview (SHI) [3] was conducted in a private room alone with a female sexual disorder therapist. Information was sought about any changes in number of sexual fantasies and arousal, and about other sexual experiences such as orgasmic and coital frequency, and enjoyment of sexual activities. Furthermore, each woman received a diary to record daily sexual events for 1 month before and during vulvar Visnadine spray use. All events considered by women as unusual and subjectively or objectively disturbing were recorded during vulvar Visnadine spray use.

A randomized 1:1, two crossover period study design was used. At the start of the study, each woman was randomly allocated into one of the two possible sequences, each consisting of two 30-day medication series: vulvar Visnadine spray on-demand/washout/daily (A sequence) and vulvar Visnadine spray daily/washout/on-demand (B sequence). Figure 1 shows the design of the study. Each woman had to apply two sprays on her clitoral area 15 min before starting sexual activity following her sexual desire on-demand phases, or every night during the daily phases of both sequences.

**Instruments**

Sexual behavior was assessed using the self-administered Female Sexual Function Index (FSFI) validated in the Italian gynecological population [14]. The total score range is 2–36. A cutoff of ≤26.55 is usually accepted for diagnosis of sexual dysfunction. Moreover, for diagnosis of sexual dysfunction, the Female Sexual Distress Scale (FSDS) was used [15]. An FSDS score of ≥15 corresponds to clinically significant distress. We considered women with an FSFI score of less than 26.55 to be affected by sexual dysfunction if they also had an FSDS score of 15 or greater.

Color Doppler sonography of clitoral blood flow was performed by using a Voluson E6 (GE Healthcare, Solingen, Germany) with a 7.5 MHz linear transducer [16]. The peak systolic velocity (PSV) and, the end diastolic velocity (EDV) were automatically calculated by the software of the Voluson E6, using the Doppler spectrum trace.

Each instrument was used at baseline (T0), before the crossover (T1) and within one week from the end of the study (T2) (Figure 1).

**Statistical analysis**

For comparisons between baseline and vulvar Visnadine spray use for FSFI scores the non-parametric Wilcoxon’s rank-sum test was used. Considering the order in which the treatments were allocated, paired Student’s t-test was performed to compare changes between baseline and vulvar Visnadine spray use for FSDS and clitoral arterial blood flow. Scores are presented as means ± SD. The result was statistically significance when \( p < .05 \). Statistical analysis was carried out using a software package for Windows 95 (Grantz SA, Primer of Biostatistics, McGraw-Hill Inc., New York, 1997).

**Results**

Fourteen women (26.8%) were excluded from the study after baseline assessment: 7 (13.4%) affected by sexual desire disorder and 7 (13.4%) for refused treatment. Consequently, 38 women...
of EDS from T0 (2.1 ± 0.9) to T1 (2.4 ± 1.1), and to T2 (4.1 ± 1.2) [T1 Vs T0, p = NS; T2 Vs T0 and T1, p < .001]. On the contrary, women on the B sequence had an increase of PSV during daily usage [T1 (14.2 ± 1.9) Vs T0 (8.2 ± 1.2), p < .001] and a decrease during on-demand usage [T2 (9.2 ± 1.2) Vs T1, p < .001; and T2 Vs T0, p = NS]. Finally, EDV increased from T0 (2.1 ± 0.8) to T1 (4.2 ± 0.6) [p < .001] and decreased at T2 (2.5 ± 0.8) [T2 Vs T0, p = NS; T1 Vs T2, p < .001].

Finally, there was a significant correlation between FSFI total score and clitoral arterial blood flow in both A (r = 0.9, p = .02) and B (r = 0.9, p = .03) sequences.

No woman reported changes of vital signs with respect to the basal values. Moreover, 1 (5.2%) woman of the A sequence reported having had spotting during daily usage of Visnadine. Transvaginal echography performed at follow-up highlighted a synchronous endometrium to the luteal phase of the cycle.

**Discussion**

This is the first study on vulvar Visnadine spray treatment of premenopausal women affected by FSAD. In fact, each woman had requested consultation for lack of clitoral sensation, lack of vaginal lubrication or for being slow to respond after sufficient sexual stimulation, with a recurrent inability to attain or maintain sufficient sexual excitement.

During genital arousal, lubrication results from increased formation of interstitial fluid from the increased blood flow through the vaginal capillary plexus subsequent to arterial dilation provoked by a good level of endogenous sexual steroids. Lubrication is induced by the autonomic nervous system and the woman is totally unaware of its occurrence [17]. It is important to note that the presence of vulvar/vaginal congestion does not always mean a woman is subjectively aroused. In fact, she has to be in an appropriate context to feel aroused.

The two-period crossover study design allowed us to obtain outcomes from each woman during treatment with on-demand or daily vulvar Visnadine spray. The major findings of our study were that women affected by FSAD, unrelated to medications, may benefit from treatment with local Visnadine spray. Visnadine was more effective when it was administrated daily than on-demand. In fact, women on the A sequence had a gradual improvement of sexual activity and quality of sexual life from on demand to daily administration. On the contrary, women on

<table>
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<tr>
<th>Table 1. Scores of the Female Sexual Function Index (FSFI) and of the Female Sexual Distress Scale (FSDS) of women using on-demand/daily (A sequence) or daily/on-demand (B sequence) vulvar Visnadine spray.</th>
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</thead>
<tbody>
<tr>
<td><strong>A Sequence</strong></td>
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<td>Desire</td>
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<td>Arousal</td>
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<td>Lubrication</td>
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<td>FSFI total score</td>
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<td>FSDS score</td>
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<tr>
<td><strong>B Sequence</strong></td>
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<tr>
<td>Desire</td>
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<td>Arousal</td>
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the B sequence had an improvement during the daily phase and a worsening during the on-demand phase.

The objective evaluation of the efficacy of vulvar Visnadine spray, measured by the color Doppler of the clitoral arterial blood flow showed a trend similar to the subjective evaluations. In fact, vascular engorgement was better during the daily than the on-demand phases of both the sequences of administration. Probably, the on-demand usage of vulvar Visnadine spray might not be enough to cause a vasocongestive response for women with FSAD, because of the low frequency of sexual activity. In fact, women on-demand administration used vulvar Visnadine spray $1 \pm 0.9$ weekly. On the contrary, women on daily administration used vulvar Visnadine spray 30 days monthly. We investigated the effects of these two modes of administration; however, it would be important to study other administration frequencies, for example two or three times a week, to understand whether the efficacy of Visnadine could be comparable to on-demand or daily administration. Therefore, in the first case it would be possible to confirm the need to use Visnadine daily; in the second case, to reduce the number of administrations while having the same effectiveness.

Our study had some limitations. The first was the small number of enrolled women, which was further reduced during the study because of drop outs. Although we observed a better efficacy with daily than on-demand administration, the small number of women cannot allow us to reach definitive conclusions. The second limitation was the lack of a placebo group. We had previously studied the effects of vasoactive drugs, such as sildenafil, either on healthy women [18] or with FSAD due to sexual genital dysfunction [19] or with diabetes [20]. Consequently, we think that future placebo controlled studies are needed to determine the efficacy of vulvar Visnadine spray in improving the quality of sexual life in a large group of women with FSAD, and in women affected by diabetes.

Acknowledgements

We wish to thank the Scientific Bureau of the University of Catania for language support.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

Ethical approval

I declare that this study was approved by the Institutional Review Board (IRB) of our Department.

Informed consent

Informed consent was obtained from all participants included in the study.

ORCID

Salvatore Caruso http://orcid.org/0000-0002-1387-0932

References