

Efficacy and safety of a new vaginal gel for the treatment of symptoms associated with vulvovaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled study

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ABSTRACT

Objective: The aim of the present randomized placebo-controlled single-center study was to assess the efficacy and safety of a new vaginal gel (Meclon Idra - Alfasigma) in the treatment of vulvovaginal atrophy (VVA). The gel is composed of sea buckthorn (*Hippophaë rhamnoides*) oil, aloe vera, 18β-glycyrrhetic acid, hyaluronic acid and glycogen. The study assessed whether the gel can reduce VVA symptoms (vaginal dryness, itching, burning sensation) and improve sexual function in postmenopausal women over 12 weeks.

Study Design: Postmenopausal women (n = 60) reporting VVA symptoms were recruited and randomized in a 1:1 ratio to the gel or placebo. Active vaginal gel or placebo was applied for 14 days and then twice a week for 90 consecutive days.

Main outcome measure: The Vaginal Health Index (VHI), including vaginal pH, was used to assess changes in objective signs, whereas the self-reported Female Sexual Function Index (FSFI) was used to investigate sexual function.

Results: Meclon Idra was effective in reducing vaginal pain, dyspareunia and vaginal pH, with the VHI showing significant improvement at day 90 (P < .0001), and in reducing each VVA symptom (vaginal dryness, vaginal itching, burning sensation) at weeks 2 and 4, and the end of the study (P < .0001). The analysis of FSFI scores showed, after the end of treatment, an improvement of sexual function in the active-treatment group, with a statistically significant increase (P < 0.001) in all domains scores and total score (P < 0.001).

Conclusions: The present single-center randomized clinical trial demonstrated the efficacy, tolerability and safety of 12-week treatment with a new vaginal gel in postmenopausal women with symptoms associated with VVA. Based on this trial, the gel seems to be a valid choice as a single, local agent for relieving VVA symptoms and improving sexual function, and to have good compliance.

This trial is registered prospectively with the Clinical Trials Registry – India, number CTRI/2019/05/01911.

Abbreviations: AE, Adverse Event; BP, Blood Pressure; CBC, Complete Blood Count; CDSCO, Central Drugs Standard Control Organization; CFR, Code of Federal Regulations; CRF, Case Report Form; CRO, Contract Research Organization; CTRI, Clinical Trial Registry-India; CV, Curriculum Vitae; Co-I, Co-Investigator; EC, Ethic Committee; GCP, Good Clinical Practice; GMP, Good Manufacturing Practice; GSM, Genitourinary Syndrome in Menopause; HR, Heart Rate; ICD, Informed Consent Document; ICF, Informed Consent Form; ICH, International Conference of Harmonization; ICMR, Indian Council of Medical Research; IEC, Independent Ethic Committee; IRB, Institutional Review Board; IP, Investigational Product; LFT, Liver Function Test; Max, Maximum; MRC, Model of End Stage Liver Disease; Min, Minimum; MRC, Medical Registration Certificate; n, Number; NA, Not Applicable; OTC, Over the Counter; PI, Principal Investigator; RBC, Red Blood Count; RFT, Renal Function Test; RR, Respiratory Rate; SAE, Serious Adverse Event; SD, Standard Deviation; SGOT, Serum Glutamic Oxalacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase; VAS, Visual Analogue Scale; VVA, Vulvovaginal Atrophy; WBC, White Blood Cell.

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1. Introduction

Among the multitude of complaints related to the lowering of estrogen in the menopause, those affecting the genitourinary tract are reported by at least 50 % of menopausal women [1–4]. The most common signs and symptoms of vulvovaginal atrophy (VVA) are dryness, dyspareunia, redness, itching, with occasional discharge and/or bleeding [5]. Recently, genitourinary syndrome of menopause (GSM) is a new definition to encompass even other sexual and urinary symptoms associated with VVA [6].

Many international surveys [7] and clinical studies indicated that the majority of women have already VVA symptoms at perimenopause/early postmenopause [8]. Interestingly, in the AGATA study, which included a sample of Italian women asking for a routine gynecological examination, a clinical diagnosis of VVA displayed a prevalence ranging from 64.7–84.2%, starting from 1 to 6 years after menopause [9].

For decades, both systemic and local low-dose estrogen therapy have been widely used for management of vaginal dryness and other symptoms associated to VVA in postmenopausal women [10–13].

The chronic nature of VVA/GSM indicates that effective treatments should preferably be prescribed at the onset of the symptoms and signs of atrophic changes of the vagina, early before severe pictures of the condition occur, and should be continued over time in order to maintain their benefits. Recently, Panay et al. [14] showed that postmenopausal women with VVA receiving treatment complained of more severe symptoms than those untreated confirming that local treatment are used too late, when VVA symptoms are already severe.

The therapeutic approach needs to be personalized and women's preferences have to be taken into account because the level of comfort with a given therapy is strongly influenced by a multitude of individual and socio-environmental factors. Non-hormonal strategies may be prescribed in women of any age who do not wish to use hormonal treatments or do show contraindications or, as a co-treatment, in those already using systemic/vaginal hormones. The prescription of vaginal moisturizers and lubricants and the maintenance of sexual activity may be helpful in improving vaginal dryness-related symptoms. However, few clinical trials assessed the efficacy of such products [15]. Lubricants are short-acting substances (water-, silicone-, or oil-based) which are useful to reduce friction during sexual activity, whereas moisturizers are

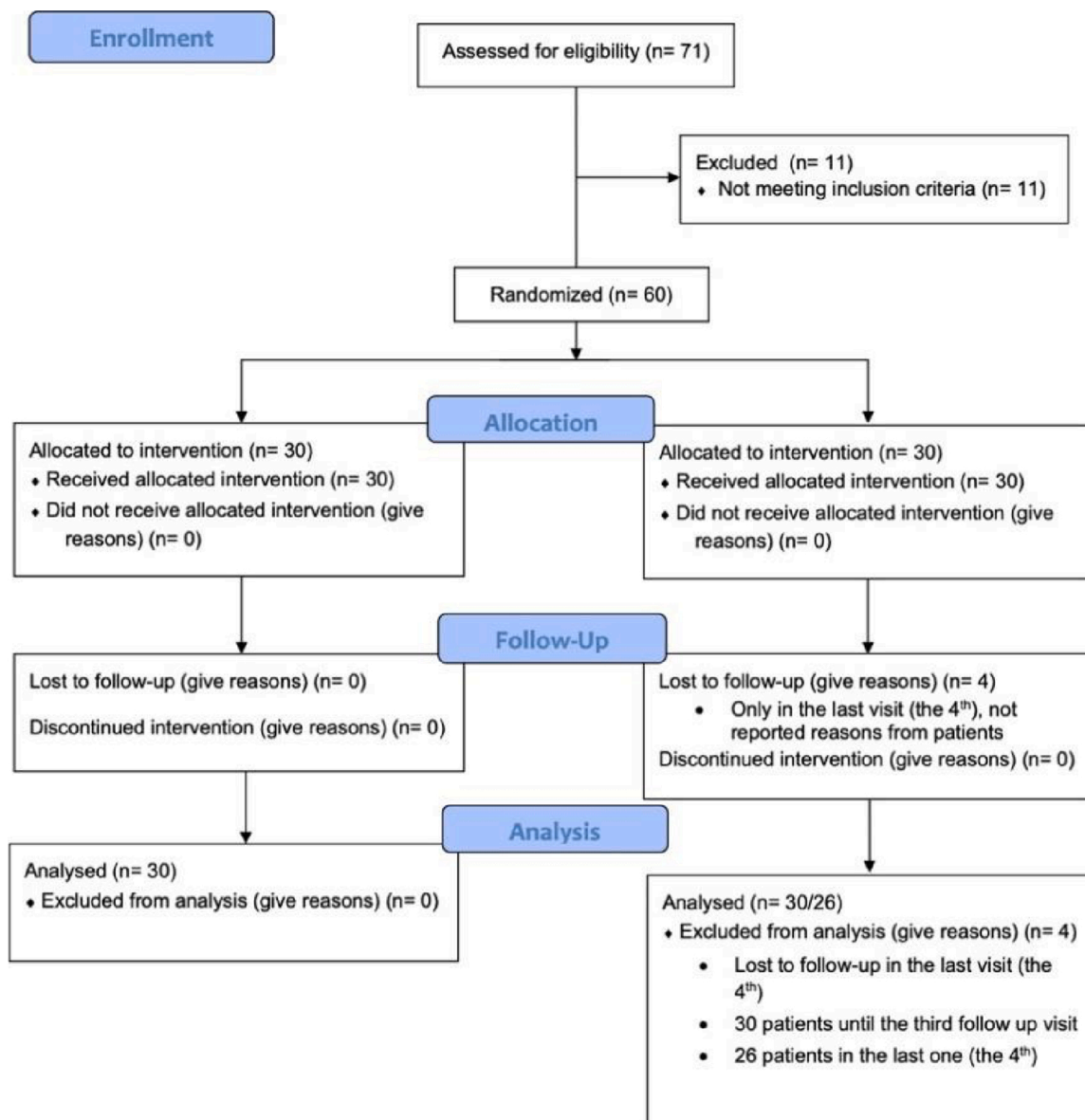


Fig. 1. CONSORT Flow Diagram.

longer acting than lubricants and may exert a trophic effect [16].

The aim of the present randomized placebo controlled single center study was to assess efficacy and safety of a new vaginal gel in postmenopausal women with VVA over 12 weeks. This new formulation (Meclon Idra Alfasigma, manufacturer Giellepi) is a gel composed of:

- a) Sea buckthorn (*Hippophaë rhamnoides*) oil, also known as sea berry oil (traditionally been as lenitive and very rich of vitamins A, B1, B12, C, E, K, and P; flavonoids, lycopene, carotenoids, and phytosterols);
- b) Aloe vera and 18 β -glycyrrhetic acid (one of the main active components of liquorice, *Glycyrrhiza glabra*) that have a documented lenitive action;
- c) Hyaluronic acid I possessing a good lubricant and soothing effect on irritated skin or mucosa;
- d) Glycogen, a substance naturally present in vaginal epithelial cells contributing to the maintenance of physiological vaginal pH.

2. Material and methods

Postmenopausal women with VVA were recruited into the study. CONSORT diagram and check-list are shown in Fig. 1. They were enrolled into the study only after they met the inclusion/exclusion criteria and with informed consent. After the initial screening period, eligible subjects were randomized in a 1:1 ratio to verum or placebo according to a randomization list computer generated using simple randomization schedule. Randomization numbers were assigned centrally through electronic Case Report Form (e-CRF) with the indication of treatment or placebo allocation.

Active vaginal gel (Meclon Idra Alfasigma / manufacturer Giellepi), or placebo, provided in single-dose vaginal dispenser/appliquer (5 ml each), was applied for 14 days and then, after 2 weeks of wash out, twice a week (at bedtime), for an overall treatment duration of 90 consecutive days (12 weeks). Study subjects were requested to attend three visits at the clinical sites (baseline and randomization, day 14, day 30 and 90 day).

The primary objective of the trial was to assess the efficacy of the vaginal gel; secondary objectives were to assess the safety, tolerability, satisfaction of this medical device as well as the impact of its use on sexual function.

The primary endpoint was:

- Change in objective signs assessed by Vaginal Health Index (VHI) on week 2, week 4 and end of the study from baseline.
 - o VHI score was assessed by an investigator including: i) vaginal overall elasticity; ii) vaginal fluid volume; iii) vaginal pH; iv) epithelial integrity; v) vaginal moisture. Each assessed on scales ranging from 1 (none) to 5 (excellent) with a total score of 25 (cut-off for VVA is 15).
- Change in subjective symptoms (recorded by each subject daily in a diary distributed at first visit for the following subjective symptoms):
 - o Vaginal dryness - 4-point scale:
 - 0 = none (symptom is not present);
 - 1 = mild (symptom is present but may be intermittent and does not interfere with activities/lifestyle);
 - 2 = moderate (symptom is present and only occasionally interferes with activities/lifestyle); and
 - 3 = severe (symptom is present and bothersome and activities/lifestyle have been modified because of it).
 - o Vaginal Itching - 4-point scale: (0 = none; 1 = mild; 2 = moderate; 3 = severe)
 - o Burning Sensation - 4-point scale: (0 absent, 1 mild, 2 moderate, 3 severe).
 - o Vaginal pH < 5

- Change in VAS scoring for Vaginal pain and Vaginal Dyspareunia {0 - (no pain) to 10 - (very severe pain)} at baseline and end of the study.

The secondary endpoints were:

- Overall treatment satisfaction questionnaire score and tolerability questionnaire (one option between: poor, fairly, good, excellent);
- Safety assessed by adverse events (AEs) reporting, Laboratory test (Blood Count, SGOT, SGPT and Serum Creatinine), Physical examination and Vital signs (Pulse rate, blood pressure and body temperature);
- Change of sexual function from baseline to the end of the study using Female Sexual Function Index (FSFI).
 - o a mean weighted-sum total score (cut-off point for female sexual dysfunction is 26.55) based on a six-item questionnaire assessing the key dimensions of sexual function (desire, arousal, lubrication, orgasm, satisfaction and pain) in women during the previous.

Efficacy was established by assessing the questionnaires (subjective) on each day of the scheduled visits (except randomization visit). FSFI and VAS scale data were collected on randomization day and on Day 90. Clinical AEs monitoring was done on each visit and complete laboratory check-ups (both hematological and biochemical) were repeated at the end of the study (day 90) in order to assess the safety of the study product. Vaginal pH determination included in the Vaginal Health Index (VHI) scoring was carried out on screening Day 14, 30 and Day 90.

2.1. Statistical and analytical plans

Study results are shown as means \pm standard deviation (SD). Both intragroup and intergroup analysis were performed in order to compare differences among the different visits and between active and placebo.

Continuous and categorical data were analysed by independent Wilcoxon rank sum test and chi-square test in order to compare the differences between active group and placebo group. The paired sample *t*-test was used to evaluate the differences in the means within each group.

Significance was set for *p*-value <0.05. All reported data on both groups were studied and no exclusion being done during analysis. The software used for statistical analysis was SAS software version 9.4

2.2. Determination of sample size

A sample size of 60 subjects, 30 in each arm (for Meclon Idra group and Placebo group); this include 27 patients calculated sample size and 3 patients (10 %) to cover dropout), is sufficient to detect a clinically important difference of 35 % between each group using a two tailed *z*-test of proportions between two groups with 80 % power and a 5 % level of significance. The overall total sample size required for the study is 60.

3. Results

We recruited sixty postmenopausal women (mean age of 57.5 \pm 4.08 years and 57.5 \pm 4.81 years in Meclon Idra and placebo group respectively) with VVA. Four patients were lost in the last follow-up in the placebo group (Fig. 1 consort).

Subject demographics and baseline characteristics at screening visit are reported in Table 1. The mean years after menopause in the active and placebo groups were 5.27 \pm 0.55 and 5.79 \pm 1.10, respectively. Mean BMI (kg/m²) in the active and placebo groups was 26.78 \pm 2.27 and 26.31 \pm 2.18, respectively.

3.1. Primary outcomes

In the active group, Meclon Idra gel was very effective in reducing vaginal pH (Table 2), with VHI showing significant improvement from baseline to final follow up; comparison between active and placebo groups at day 90 by Wilcoxon Signed rank-sum test showed a statistical

Table 1
Demographic and baseline characteristics.

Parameter/Statistics	Active	Placebo
Age (Years)		
N	30	30
Mean (SD)	57.5(4.08)	57.5(4.81)
Median	57.0	58
Min, Max	50.65	50.65
Sex, n (%)		
Female	30(100.0)	30(100.0)
Male	0(0.0)	0(0.0)
Menopausal Staus – years after post menopause		
N	30	30
Mean (SD)	5.27(0.546)	5.79(1.105)
Median	5.00	6.00
Min, Max	4.6, 6.2	4.0, 8.0
Height		
N	30	30
Mean (SD)	165.0(5.16)	165.0(3.45)
Median	166.0	165.0
Min, Max	157, 174	159, 173
Weight		
N	30	30
Mean (SD)	72.84(6.486)	71.70(6.656)
Median	71.75	71.50
Min, Max	61.0, 84.0	58.5, 84.0
BMI		
N	30	30
Mean (SD)	26.78(2.270)	26.31(2.180)
Median	26.98	26.07
Min, Max	22.8, 31.2	23.1, 30.5

Table 2
p-value for Change in Vaginal pH scoring.

	Active		Placebo		p value
	pH > 5	pH ≤ 5	pH > 5	pH ≤ 5	
screening	100	0	100	0	0
Visit 5	20	80	100	0	<0,001
p value	<0,001	<0,001	0	0	

Note: P-value was estimated using Wilcoxon Signed rank sum test.

difference with very high significance (<.0001) (Table 3, Fig. 2). Each vaginal symptom (dryness, itching, burning sensation) assessed on week 2, 4 and at the end of the study was strongly reduced in the active group as compared to placebo with a statistically significant (p < 0.0001) change (see vaginal dryness in Fig. 3). A significant improvement (p < 0.0001) in both vaginal pain and dyspareunia (Fig. 4) scoring was observed in the subjects on active treatment at the end of the study period.

3.2. Secondary outcomes

3.2.1. Satisfaction with treatment and its tolerability

Almost all subjects who were in the active group reported excellent tolerability of vaginal gel and declared themselves happy or very happy for: satisfaction with current treatment, convenience, improvement of their medical condition, rating compared to their previous treatment, the recommendation to others and continuation of their treatment.

Table 3
p-value: Change in objective symptoms assessed by Vaginal Health index on week 2, week 4 and end of the study from baseline.

Visit	Mean value ± SD	p-value
Baseline	7.9 ± 1.49	/
Change from Baseline to Visit 3	16 ± 1.33	<.0001
Change from Baseline to Visit 4	18.5 ± 1.38	<.0001
Change from Baseline to Visit 5	20 ± 1.89	<.0001

Note: P-value was estimated using Wilcoxon Signed rank sum test.

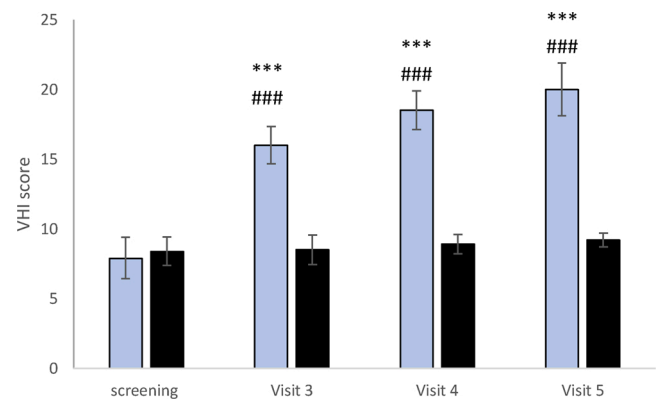


Fig. 2. Vaginal Health Index (VHI) score. Mean values and SD. Blue bars: Meclon Idra; Black bars: placebo. ***P < 0.001 Meclon Idra vs baseline; ### P < 0.001 Meclon Idra vs Placebo.

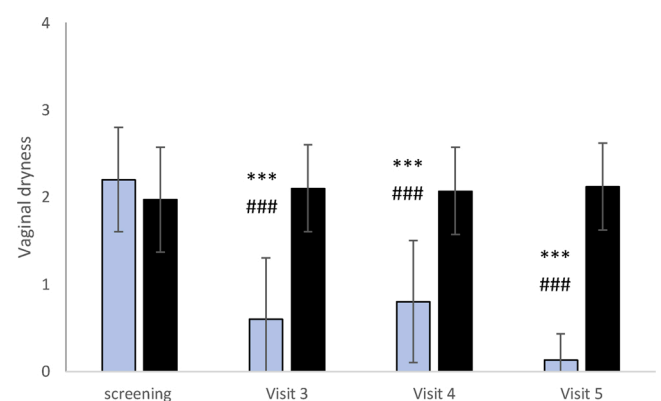


Fig. 3. Vaginal dryness. Mean values and SD. Blue bars: Meclon Idra; Black bars: placebo. ***P < 0.001 Meclon Idra vs baseline; ###P < 0.001 Meclon Idra vs Placebo.

3.2.2. Safety with treatment

The assessment of AEs and data collected by laboratory test, physical examination and vital signs confirmed the safety of the tested product.

In particular, 2 subjects reported an AE on Visit 3: Severe Burning and Itching in Vagina after using Meclon Idra. These AEs resolved without medications.

None of the enrolled subjects had abnormality in physical findings on the screening visit or during the study visits. No statistically significant changes in vitals (Systolic BP, Diastolic BP, Pulse rate, Respiratory Rate and Temperature) observed between baseline and visit 5 or between the treatment groups. All laboratory parameters showed no clinical significance and the study product was found to be safe after the treatment period.

3.2.3. Impact on sexual function (female sexual function index-FSFI questionnaire)

At visit 5 (day 90), the analysis of the scores related to FSFI showed an improvement of sexual function in the active group, with a statistically significant increase (P < 0.001) of all domains scores and total score (P < 0.001), whereas no statistically significant variations were observed compared to baseline in the placebo group (Fig. 5).

In particular, at the 90-days follow-up (Visit 5), among women assigned to the treatment group, 83 % reported a high or moderate level of sexual desire. Moreover, about 47 % reported a high or moderate sexual arousal during sexual intercourse and 23 % and 20 % indicated high difficulties to obtain or maintain lubrication, respectively. Only 26.7 % of women belonging to the treatment group referred to have high difficulties in achieving orgasm and 46.7 % of them declared high or

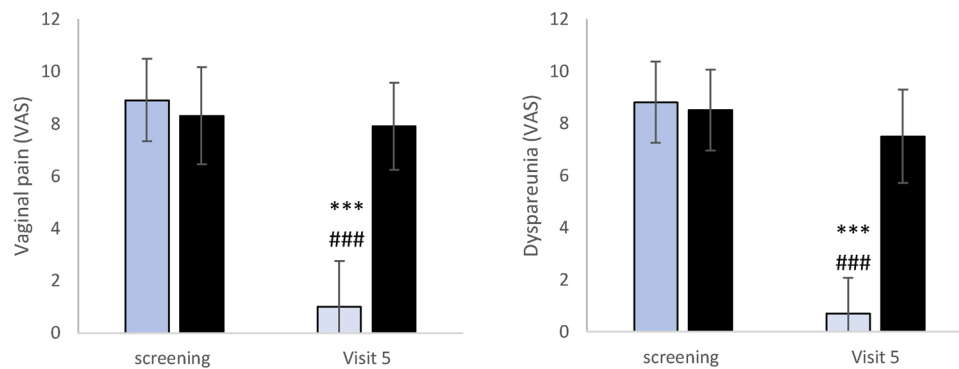


Fig. 4. Vaginal pain and dyspareunia. Mean values and SD. Blue bars: Meclon Idrá; Black bars: placebo. *** $P < 0.001$ Meclon Idrá vs baseline; ### $P < 0.001$ Meclon Idrá vs Placebo.

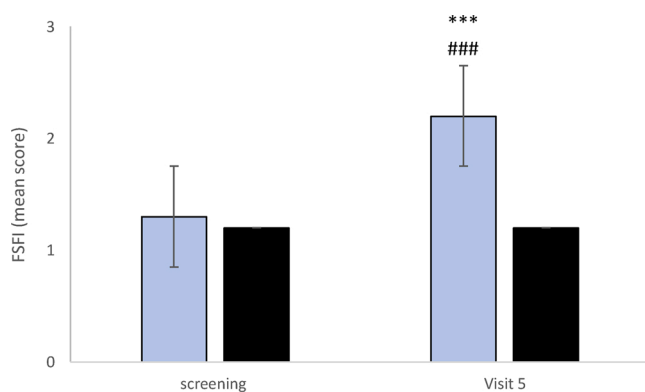


Fig. 5. Female sexual function index FSFI. Mean values. Blue bars: Meclon Idrá; Black bars: placebo. *** $P < 0.001$ Meclon Idrá vs baseline; ### $P < 0.001$ Meclon Idrá vs Placebo.

moderate grades of dissatisfaction for sexual relationship with their partner. Finally, 10 % of women reported high or very high levels of discomfort or pain during or following vaginal penetration.

Overall, the percentage of women who reported no sexual activity in the past 4 weeks did not change and remained around 30 % in both groups.

4. Discussion

The present randomized, controlled, open-label study demonstrated that a 12-week local application of a gel Meclon Idrá containing Sea Buckthorn, Aloe Vera, 18 β - glycyrrhetic acid, Hyaluronic Acid and Glycogen, was able to improve significantly vaginal dryness and other symptoms and it can be another effective option to relieve VVA.

Due to increasing longevity, women may now suffer from VVA for over one-third of their life [17,18]; associated symptoms can be very troublesome, especially for those who are younger and in partnership [19].

The choice of a therapy depends on symptoms severity, on treatment effectiveness and safety, and on patient preference [20].

Estrogen therapy, either vaginal, in low doses, or systemic, remains the therapeutic standard for symptomatic women who suffer from moderate to severe VVA, and for those who do not sufficiently improve with the use of lubricants or moisturizers. [21].

Therefore, VVA/GSM remains under diagnosed and under treated, usually becoming very severe [22]. Use of intravaginal testosterone [23], or new class of drugs, like selective estrogen receptor modulators (SERMs), can offer a safe, effective and alternative treatment of VVA. They are synthetic nonsteroidal agents that exhibit tissue-specific estrogens' receptor (ER) agonist or antagonist activity [24]. Finally,

energy-based devices, especially laser therapy, have been introduced as a non-hormonal option for the treatment of VVA, but according to a recent best practice consensus document [25] we need further clinical data for high level and long-term evidence regarding its safety and efficacy.

That being so, all Scientific Societies dealing with postmenopausal health and quality of life of BCSs [22,26] report that the first-line therapies include vaginal moisturizers, continued sexual activity, and lubricants. Lubricants and moisturizers are used for sexual comfort and pleasure and are particularly useful for women with mild to moderate vaginal dryness and for those who are not candidate to use vaginal ET whether for medical reasons or personal preference.

Lubricants provide short-term relief of vaginal dryness and discomfort with sexual activity. [27]. Instead, vaginal moisturizers are used on a regular basis to maintain vaginal moisture (daily or every 2–3 days as needed according to symptom severity). They provide longer-term relief by increasing mucosal moisture and reducing pH. Sometimes vaginal lubricants and moisturizers are applied as needed in combination with other GSM treatments.

Over-the-counter vaginal moisturizers and lubricants can ease the symptoms of VVA. However, their chemical composition varies enormously and some are known to cause detrimental effects due to unphysiological pH, osmolality, and additives [28].

Clinical Data suggesting improvement in genitourinary symptoms with non-hormone treatments are sparse, and to date, there are no adequately powered, randomized, doubleblind, placebo-controlled studies directly comparing low-dose vaginal estrogen therapies or vaginal DHEA with commonly used nonhormone treatments [29].

In our RCT trial, all primary and secondary outcomes were significant, also showing the safety of the medication.

Meclon Idrá gel improved not only objective symptoms but also reduced subjective symptoms throughout the study when compared with placebo in a statistically significant manner; in particular, it i) improved VVA symptoms of burning, dryness and itching; ii) reduced vaginal pH, iii) reduced VAS score of both dyspareunia and vaginal pain. Furthermore, patients reported a significant overall treatment satisfaction and tolerability assessed on week 12 and only 2 subjects reported AEs.

The positive impact on Meclon Idrá gel on several dimensions of sexual response is relevant; in fact, low desire, arousal and orgasmic dysfunction due to VVA with or without sexual pain affect postmenopausal women. Therefore, the amelioration of low desire with Meclon Idrá can be explained by its effectiveness on VVA [30].

There is a tendency to assume that postmenopausal women are less sexually active and have decreased sexuality. However, most healthy women remain sexually active well into advanced age, even though physiological changes associated with menopause play a significant role in the pathogenesis of sexual disorders [31]. The overall prevalence of sexual dysfunctions at menopause is estimated between 68 % and 86.5

%, depending on cultural, religious, ethnic, and individual differences [32] and GSM is the most important cause of genito-pelvic pain disorders [33,34]. Around 50–60 % of post-menopausal women declare that vaginal discomfort has a negative impact on their sex life or on their relationship with their partner or on their social life [33,35,36].

Results of comparative analyses of this trial are limited because of the used diagnostic methods of VVA (no cytological vaginal maturation index results of vaginal samples), the small sample sizes and the short follow up at 3 months. Larger groups of patients with longer clinical follow up need to be further studied and comparative studies with other active compounds have to be designed.

Nevertheless, to date, this new formulation seems to be attractive as a single local agent for the treatment of VVA associated symptoms. Greater patient acceptance of such vaginal gel could translate into a better compliance, which is essential to counteract the chronicity of the condition over time.

Contributors

Francesco De Seta participated in the designing of the trial.

Salvatore Caruso participated in the critical revision of the manuscript.

Giovanni Di Lorenzo participated in the export of the data.

Federico Romano participated in the critical revision of the manuscript.

Mariateresa Mirandola participated in the final submission of the manuscript.

Rossella E. Nappi participated in the critical revision of the manuscript.

All authors saw and approved the final version of the paper.

Conflict of interest

Francesco De Seta had past financial relationships (lecturer, member of advisory boards and/or consultant) with Bayer HealthCare AG, Giellepi, Uniderm.

Rossella E. Nappi had past financial relationships (lecturer, member of advisory boards and/or consultant) with Boehringer Ingelheim, Ely Lilly, Endoceutics, Gedeon Richter, HRA Pharma, Procter & Gamble Co, TEVA Women's Health Inc and Zambon SpA. At present, she has ongoing relationship with Astellas, Bayer HealthCare AG, Exceltis, Fidia, Merck Sharpe & Dohme, Novo Nordisk, Palatin Technologies, Pfizer Inc, Shionogi Limited and Theramex.

All other authors declare that they have no conflict of interest.

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Ethical approval

Ethical approval was provided by Rajalakshmi Hospital Institutional Ethics Committee. This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki that was consistent with GCP, ISO 14155 and applicable regulatory requirements. The rights, safety and well-being of the trial subjects in this study were the most important considerations and prevailed over interests of science and society. This trial was conducted in compliance with the protocol, which received prior Ethics Committee (EC) approval. Every individual involved in conducting this trial was qualified by education, training, and experience to perform his / her respective task(s). Voluntary informed consent was obtained from every subject prior to participation in the clinical trials. All clinical trial information was

recorded, handled, and stored in a way that allowed its accurate reporting, interpretation and verification. The confidentiality of records that could identify subjects was protected, respecting the privacy in accordance with the applicable regulatory requirements. Investigational products that were manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP) were used in accordance with approved protocol and proper documentation was kept. This trial is registered prospectively with the Clinical Trials Registry – India, number CTRI/2019/05/01911.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

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

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