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Original Article

Vaginal health and quality of sexual life of postmenopausal women on hyaluronic acid and Biosaccharide Gum-1 vaginal gel

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ABSTRACT

Objective: To evaluate the efficacy of daily vaginal gel containing hyaluronic acid (HA) and Biosaccharide Gum-1 (BG-1) on vulvovaginal atrophy (VVA) and on sexual function and quality of life (QoL).
Materials and methods: One hundred-four postmenopausal women with VVA were enrolled in the nonrandomized comparison cohort study. Of them, 50 women on HA/BG-1 participated in the study group and 54 women on lubricants/moisturizers on-demand as a control group.
The primary endpoint was the efficacy of the vaginal gel on VVA evaluated by the Vaginal Health Index (VHI) score. Secondary endpoints included sexual behavior by the self-administered female sexual function index (FSFI) questionnaire, and quality of life (QoL), by the Short Form-36 questionnaire (SF-36).
Results: All symptoms of AVV improved after 12 weeks of treatment in women on HA/BG-1. The VMI, although improved at the 12-week follow-up compared to baseline, it connoted a low estrogenic stimulation value. Sexual function improved significantly in women on HA/BG-1. Moreover, women reported a significant improvement in the somatic aspects of QoL. No benefits were obtained by the women in the control group.
Conclusions: Treatment with HA/BG-1 could have used in postmenopausal women who complain of vaginal dryness. The amelioration of VVA-related signs could improve sexual function and QoL.

Introduction

Postmenopausal women are likely to have vulvovaginal disorders due to the cessation of ovarian estrogenic activity [1]. About 50% of postmenopausal women experience vulvovaginal atrophy (VVA) with moderate or severe symptoms affecting their quality of life and sexual function [2–4].

The discomforts most reported by women are dyspareunia, vulvovaginal burning, foul-smelling vaginal discharge, bleeding during intercourse, or dysuria [5], which are symptoms of the genitourinary syndrome (GSM) [6].

Symptoms can be more disabling if menopause has been induced for medical reasons, such as following chemotherapy or anti-estrogen therapies, or oophorectomy [7]. Additionally, metabolic disease or reduced sexual intercourse are risk factors for VVA. Symptoms are strictly due to changes in trophism, microbiota, and vaginal pH [8].

Sexual function can have a dysfunctional reason, following dyspareunia, which not infrequently affects sexual desire. In fact, women suffering from dyspareunia could lead to libido reduction [9].

Medical treatments are usually based on the administration of estrogen [10,11], or DEHA [12] by the vaginal route, or on oral selective estrogen receptor modulators (SERMs) [13].

However, postmenopausal women do not always accept hormonal treatments, choosing natural approaches where possible [14]; the use of moisturizers and lubricants, frequently on demand, are widely adopted by women who are afraid of using hormonal treatments or who have contraindications to using them [15,16].

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In this case, non-hormonal treatments via the vagina should usually be effective and well-tolerated, and this depends not only on their composition but also on osmolarity and pH, and on having a physiological appearance similar to natural vaginal secretions. Hyaluronic acid (HA) is a common component of non-hormonal aids, because of its ability to repair the processes of vaginal atrophy and dystrophy and to allow sufficient vaginal hydration [17,18].

The aim of this nonrandomized comparison cohort study is to evaluate the efficacy of the vaginal gel containing HA and Biosaccharide Gum-1 (BG-1) (Vidermina Intima Mucus ®, Istituto Ganassini SpA, Milan, Italy) in postmenopausal women with VVA (primary endpoint), and the effects on the vaginal maturation index (VMI), sexual function and quality of life (QoL) (secondary endpoints). HA is characterized by a high molecular weight that does not allow it to penetrate deeply into the vaginal epithelium. Therefore, it carries out a moisturizing and protective film action on the surface of the vaginal epithelium, reducing genital dryness. In fact, thanks to its ability to distribute itself on the surface, it forms a film that hinders the loss of trans-epidermal water. It also assists the repair processes of the vaginal mucosa in cases of atrophy and reduces symptoms such as itching and burning. These activities are supported by both an osmolarity of less than 380 mOsm/Kg and a pH of 4.2 as recommended by the Advisory Note "Use and procurement of additional lubricants with male and female condoms: WHO/UNFPA/FHI360" [19]. BG-1 is a film-forming polysaccharide rich in L-Fucose, D-Galactose, and Galacturonic Acid. It is an anionic polysaccharide of biotechnological origin that is produced by bacterial fermentation of plant-based substrates. BG-1 stimulates the production of Sirtuin-1, an inhibitor of the synthesis of inflammation mediators. In association with L-Fucose, it inhibits neurogenic inflammation [20]. It gives the gel soothing and moisturizing properties. Other ingredients include gelling agents, preservatives, and water.

Materials and methods

The study was conducted at the Menopause Service of the Gynecological Clinic, Department of General Surgery and Medical Surgical Specialties, University of Catania, Italy. The study protocol complies with the guidelines of the Declaration of Helsinki of 2013 and was approved by the Ethics Committee Catania 1, n. 84/2020/PO.

The study was carried out from May 2020 to July 2021. Each woman was informed in advance about the objectives of the study. Each woman was asked to read and sign the study's Informed Consent; none of them received any monetary compensation.

Postmenopausal women for 1 year, or women with amenorrhea for 6 months with menopausal values of Estrogen and FSH; with symptoms and signs of VVA, and with disorders of sexual function were invited to participate in the study.

Surgical or pharmacological postmenopausal women or women with abnormal vaginal bleeding; diagnosed with endometrial thickening $\geq$ 4 mm, by transvaginal ultrasound; who had been on hormonal treatment up to 3 months before enrollment; who had contraindications to the use of local treatments due to previous intolerance; or with a partner suffering from sexual dysfunction, were excluded from the study.

One hundred four women gave consent to participate in the nonrandomized comparison cohort study. Of these, 50 were allowed to take part as a study group and 54 refused the use of the daily vaginal gel, choosing to use lubricants/moisturizers on demand. The latter gave their consent to participate as a control group.

Instruments

The vaginal health index (VHI) was used for the objective investigation of vaginal hydration and secretions, the elasticity and appearance of the vaginal mucosa, and finally for the detection of vaginal pH [21]. Changes in vaginal pH greater than 5.0 have been associated with a decrease in serum estradiol [22]. Indeed, a pH of 5–5.49 could be indicative of mild atrophy, a pH of 5.5–6.49 of moderate atrophy, and a pH above 6.5 of severe atrophy, in the absence of infection [23]. Each of these 5 items is evaluated by means of a scale from 1 (none) to 5 (excellent) and then the average of the scores is calculated. A value of $\leq$15 (= cut-off) is generally considered for the diagnosis of low vaginal health.

The vaginal maturation index (VMI) was used to quantify the parabasal, intermediate and superficial cells of the vaginal epithelium, by means of vaginal cytological sampling with the subsequent calculation of the percentage of the cell type [24]. The VMI is obtained through the formula [1 (% superficial cells)] + [0.6 (% intermediate cells)] + 0.2% (parabasal cells)]. Values from 20 to 49 indicate low, 50 to 64 moderate, and 65 to 100 high estrogenic stimulation [25].

Sexual behavior was assessed using the self-administered female sexual function index (FSFI) validated in the Italian gynecological population of childbearing age [26]. The FSFI consists of six domains, namely desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia, which are measured on a five-point Likert scale, ranging from 0 (no sexual activity) or 1 (never/very low) to 5 (always/very high). A score is calculated for each of the six domains and the total score is obtained by adding all the elements. The total score range is from 2 to 36. A value of $\leq$26.55 (= cut-off) is generally considered for the diagnosis of sexual dysfunction. In addition, to confirm sexual dysfunction, it is necessary for it to cause significant personal distress to the woman.

Therefore, the 12-item Female Sexual Distress Scale (FSDS) questionnaire was used, with a maximum score of 48. An FSDS score $\geq$15 corresponds to clinically significant distress [27]. In summary, women with an FSFI score of $\leq$26.55 are considered to have sexual dysfunction if they have an FSDS score $\geq$15.

The assessment of the quality of life (QoL) was measured by the Short Form-36 questionnaire (SF-36) [28]. The questionnaire contains 36 questions that group four categories of somatic aspects [physical activity, physical role, somatic pain, and general health] and four mental aspects [vitality, social activity, emotional role, and mental health]. The women were asked to enter a score on a scale of 0–100 for each item that best matched their awareness. Subsequently, the sum of all the elements of each category was performed. As a result, total somatic and mental health scores were obtained; higher scores indicate better QoL.

Each woman had a diary in which to note the frequency of sexual activity and any new event that they wanted to report.

Each questionnaire or instrument was used at enrollment (baseline) and at the 12th week of treatment (follow-up).

Treatment

Each woman in the study group was asked to self-administer 2 doses of 3 cm of the vaginal gel, equivalent to 0.5 g, daily. In addition, women were asked to self-administer a total of 12 cm of gel, equivalent to 1 g, before intercourse. The control group consisted of women who were using lubricants or moisturizers on demand.

Statistical analysis

Assuming a standard deviation of 2 and a mean difference of 2 with a $p \leq 0.05$ for the primary outcome measure (VHI), as reported from similar studies [29], the sample size calculation indicated that 100 subjects would be the minimum number to have 50 women for each study arm required to have 90% statistically significant power.

The chi-square and ANOVA tests were used to compare the demographic and clinical data between the two groups at baseline, respectively. The difference was estimated with a 95% confidence interval (CI). Paired student's t-test was used to compare the values obtained at baseline with those of the follow-up from the VHI, VMI, FSDS, and SF-36 domains. For comparisons of the values obtained from the FSFI items between the baseline and the follow-up, the nonparametric Wilcoxon rank-sum test with z values was used. The correlation analyses with Pearson's r coefficient were performed to examine the relationships between the VHI and FSFI scores. Scores are presented as mean ± SD. The result was statistically significant when $p < 0.05$. Statistical analysis was carried out using the Primer of Biostatistics statistical computer package (Glantz SA, New York, USA: McGraw-Hill, Inc. 1997).

Results

Table 1 shows the demographic characteristics of the study group and control group at baseline. Women of both groups were used to using on-demand lubricants or moisturizers ($p = 0.51$).

After enrollment, 8 (16%) women in the study group were excluded from the statistical evaluation as they did not complete the study. On the other hand, 18 (33.3%) women in the control group dropped out of the study. Consequently, 42 (84%) and 36 (66.7%) women in the study and control group, respectively, completed the study.

In the study group, 15 (35.7%) women performed a typical administration of the vaginal gel, discontinuing it on average once a week. The remaining 27 (64.3%) women performed perfect administration of the vaginal gel.

Intragroup vaginal health changes are shown in Fig. 1. The study group had an improvement in the VHI from the baseline to the follow-up (8.6 ± 3.3 Vs 18.8 ± 2.3, $p < 0.0001$; +118.6% Vs baseline); on the contrary, the control group did not obtain any benefit from on-demand administration (9.8 ± 3.2 Vs 11 ± 2.3, $p = 0.28$; +12.2% Vs baseline).

Table 2 shows the changes of each VHI item of both groups and the intergroup statistical analysis at baseline and at the 12-week follow-up.

Particularly, in the study group, vaginal secretion improves more evidently (+300%) than, in order, pH (+200%), hydration (+100%), the appearance of vaginal mucosa (+100%), and finally vaginal elasticity (+50%). The pH decreased from a value > 6 (severe atrophy) to a value between 5.1 and 5.5 (mild to moderate atrophy). The control group did not experience any benefit in each VHI item.

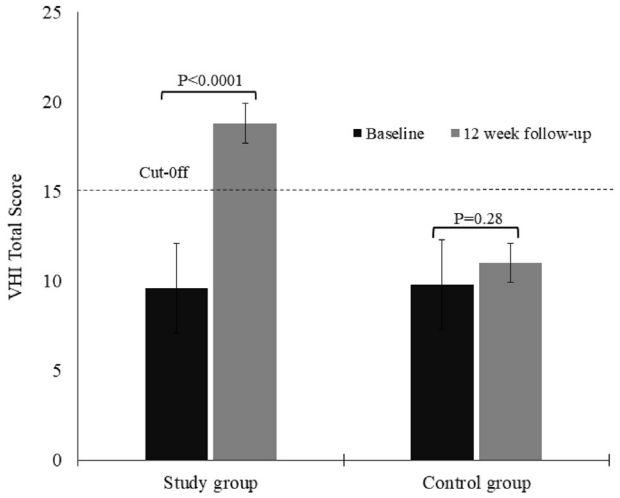

Fig. 1. Intragroup comparison of vaginal health index (VHI) of postmenopausal women treated with hyaluronic acid (study group) or using on-demand lubricants or moisturizers (control group).

The VMI had a similar trend (Fig. 2).

The women in the study group had an improvement in the total score (32.8 ± 3.1 Vs 47.3 ± 3.4, $p < 0.0001$; +44.2%); however, the score meant low estrogenic stimulation. The control group underwent no VMI modification (33.6 ± 2.9 Vs 33.9 ± 3.2, $p < 0.41$).

Table 3 shows the VMI intergroup statistical analysis at baseline and at the 12-week follow-up. The study group had a significant reduction of basal and parabasal cells ($p < 0.0001$), and an improvement of intermediate and superficial cells ($p < 0.0001$) at the 12-week follow-up compared to baseline. Specifically, the percentage of parabasal cells was reduced by 50%, and that of intermediate cells increased by 80.1%, from baseline to 12-week follow-up. Moreover, the percentage of superficial cells was 7.1 at follow-up compared to 0% at baseline. The control group did not have any benefit.

Fig. 3 shows changes in women's sexual function and sexual distress levels at baseline and follow-up. The FSFI score in the study group, although it did not reach the cut-off (≤26.55), improved from 17.2 to 22.3 ($p < 0.001$), meaning an improvement of 29.6%.

The items that contributed to the improvement of the FSFI of the study group during the use of the vaginal gel were mainly lubrication ($p < 0.0001$), arousal ($p < 0.009$), dyspareunia ($p < 0.009$) and satisfaction ($p < 0.009$). The level of desire ($p < 0.2$) and

Table 1
Demographic and clinical characteristics at baseline.

	Study Group (n = 50)	Control Group (n = 54)	P
Mean Age (±SD)	55.6 ± 4.2	54.9 ± 4.1	0.39 (ANOVA)
BMI, kg/m^2 (±DS)	26.8 ± 4.8	25.7 ± 5.6	0.28 (ANOVA)
Age at menopause (years)	51.5 ± 3.6	50.7 ± 2.6	0.74 (ANOVA)
Years from menopause	5.3 ± 1.9	5.6 ± 1.4	0.35 (ANOVA)
Parity, n. (%)			(χ^2 test)
One child	9 (18)	11 (20.3)	0.03
Two or more children	41 (82)	43 (79.6)	0.9
Smoking habit, n. (%)			(χ^2 test)
Never smoked	36 (72)	38 (70.3)	0.88
Smoker	11 (22)	10 (18.5)	0.8
Ex smoker	3 (6)	6 (11.2)	0.09
Lubricants/Moisturizers, n. (%)			(χ^2 test)
On demand	32 (64)	41 (75.9)	0.51
Hormonal treatment in the past, n. (%)	7 (14)	5 (9.3)	(χ^2 test) 0.39

orgasmic experience ($p < 0.1$), although improved, did not reach statistical significance (Table 4).

At the same time, the FSDS decreased, from a dysfunctional value of 17.8 to a normality value of 13.7 ($p < 0.001$), meaning a 23% reduction. On the other hand, the control group did not have any change in FSFI ($p = 0.21$) and FSDS ($p = 0.83$) scores.

Moreover, the FSFI scores demonstrated a negative correlation with VHI values ($r -0.99$; $p < 0.004$).

Finally, Fig. 4 shows the QoL, investigated by the SF-36 questionnaire, that fundamentally improved from 57.5 to 65.6 ($p = 0.007$, +14% Vs baseline)in aspects related to somatic health. The total mental health score in the study group improved to the limit of statistical significance [58.9 Vs 64.5 ($p = 0.05$); +9.5% Vs baseline]. The control group had no somatic health ($p = 0.89$) and mental health ($p = 0.45$) total score changes.

Each woman recorded her frequency of coital activity in the daily diary. The study group reported an increase from 1 ± 0.5 to 3 ± 0.7 sexual intercourse per month ($p < 0.001$). On the other hand, the control group had no increase in frequency (1 ± 0.7 to 1 ± 0.3, $p = 1$). No women reported adverse events during the administration of the vaginal gel.

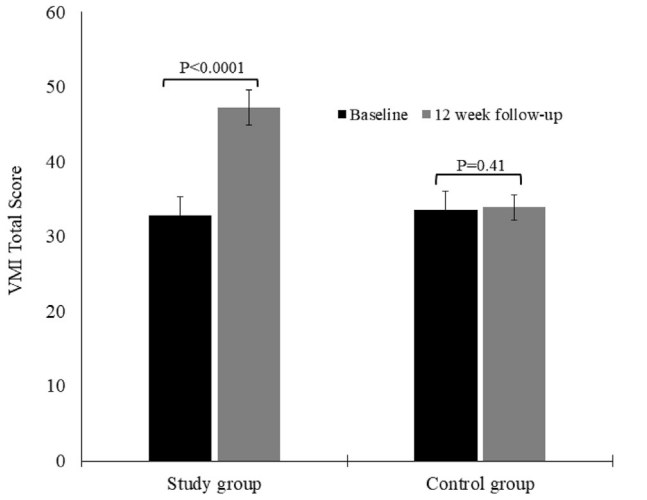

Fig. 2. Intragroup comparison of vaginal maturation index (VMI) of postmenopausal women treated with hyaluronic acid (study group) or using on-demand lubricants or moisturizers (control group).

Discussion

The current nonrandomized comparison cohort study aimed to measure the effectiveness of HA/BG-1 in a gel formulation administered vaginally to postmenopausal women with VVA. An improvement in both the primary endpoint - vulvovaginal symptoms and vaginal well-being - and the secondary endpoints - vaginal epithelial trophism, quality of sexual function, and QoL-were observed.

The symptoms of VVA showed benefits after 12 weeks of treatment in women using HA/BG-1 vaginal gel compared to the control group.

With respect to the secondary endpoints, the VMI in the study group reached values showing no estrogen-dependent maturation of the vaginal epithelium. In fact, the maturation index, although improved at the 12-week follow-up compared to baseline, connoted a low estrogenic stimulation value. This improvement may depend, in order, on the effectiveness of the HA/GM-1 daily usage and the increased coital frequency; the latter in itself promotes an activation/stretching of the vaginal muscle epithelium layers with consequent neuro-vascular activation [30]. Differently, women in the control group, using lubricants or moisturizers on demand, did not undergo similar improvement. With regard to the individual items of sexual function whose scores the FSFI measures, lubrication was the subjective aspect that improved more significantly than the other items. Therefore, it was possible to highlight an overall improvement in vaginal well-being, both through the VHI - which allows for the measurement of the objective aspects of vaginal health - and through the FSFI - which defines the degree of subjective well-being of sexual health.

Simultaneously, pain syndrome decreased; the reduction in dyspareunia probably promoted an increase in coital frequency that was not due to an increase in sexual desire. Interestingly, the reduction in pain syndrome could be due to the synergistic activity between HA trophic effects and BG-1 inhibition of the synthesis of inflammation mediators and of neurogenic inflammation. These treatment benefits were not observed in the control group. To strengthen the effectiveness of the treatment adopted, the women reported a more significant improvement in the somatic aspects than the mental health of QoL.

There are many studies on HA for the treatment of genital urinary symptoms in postmenopausal women. However, the gel that we used, unlike others, contains BG-1 having anti-inflammatory activity. It is a polysaccharide rich in L-Fucose, which inhibits neurogenic inflammation. The channels activated by inflammatory agents are numerous, and usually, their activation increases intracellular calcium in neurons. The polysaccharide L-Fucose has an anti-inflammatory effect, which previously was confirmed by the decreased neuropeptide substance P release -an inflammatory mediator-, which is released after a cytosolic calcium influx (20). The synergistic activity of HA (reducing genital dryness), and BG-1

Table 2
Intergroup statistical analysis of each vaginal health index (VHI) item at baseline and 12-week follow-up.

VHI Items	Baseline			12-week follow-up		P[a]
	Study Group n.50	Control Group n.54	P[a]	Study Group n.42	Control Group n.36	
Moisture	2 ± 1.1	2.2 ± 1.6	0.46 95% CI, −0.73 to 0.33	4 ± 1.5	2.1 ± 1.2	<0.001 95% CI, 1.20 to 2.59
Secretion	1 ± 0.8	1.1 ± 0.5	0.44 95% CI, −035 to 0.15	4 ± 1.2	2.2 ± 0.9	<0.001 95% CI, 0.94 to 2.65
Elasticity	2 ± 1.2	1.9 ± 1.3	0.68 95% CI, −0.38 to 0.58	3 ± 1.1	1.6 ± 1.1	<0.001 95% CI, 0.85 to 1.94
Appearance	2 ± 0.5	1.8 ± 1.2	0.27 95% CI, −0.16 to 0.56	4 ± 1.6	1.5 ± 1.1	<0.001 95% CI, 1.78 to 3.21
pH	1 ± 1.2	1.1 ± 0.7	0.60 95% CI, −0.47 to 0.27	3 ± 1.4	1.2 ± 0.5	<0.001 95% CI, 1.22 to 2.37

[a] Two-sided t test; CI= Confidence Interval.

Table 3
Intergroup statistical analysis of the vaginal maturation index (VMI) at baseline and at the 12-week follow-up.

VMI % Cells	Baseline		P[a]	12-month follow-up		P[a]
	Study Group n.50	Control Group n.54		Study Group n.42	Control Group n.36	
Basal	7.2 ± 1.9	6.8 ± 1.6	0.24 95% CI, −0.28 to 1.08	0.1 ± 1.1	5.2 ± 2.8	<0.0001 95% CI, −6.06 to −4.13
Parabasal	57.1 ± 4.2	58.3 ± 4.8	0.17 95% CI, −2.96 to 0.56	28.5 ± 3.9	57.5 ± 3.7	<0.0001 95% CI, −30.9 to −27.1
Intermediate	35.7 ± 2.5	34.9 ± 2.9	0.13 95% CI, −0.25 to 1.85	64.3 ± 5.6	37.3 ± 3.1	<0.0001 95% CI, 26.69 to 29.4
Superficial	0	0	1 95% CI, −0.18 to 1.18	7.1 ± 1.6	0	<0.0001 95% CI, 6.38 to 7.81

[a] Two-sided t test; CI= Confidence Interval.

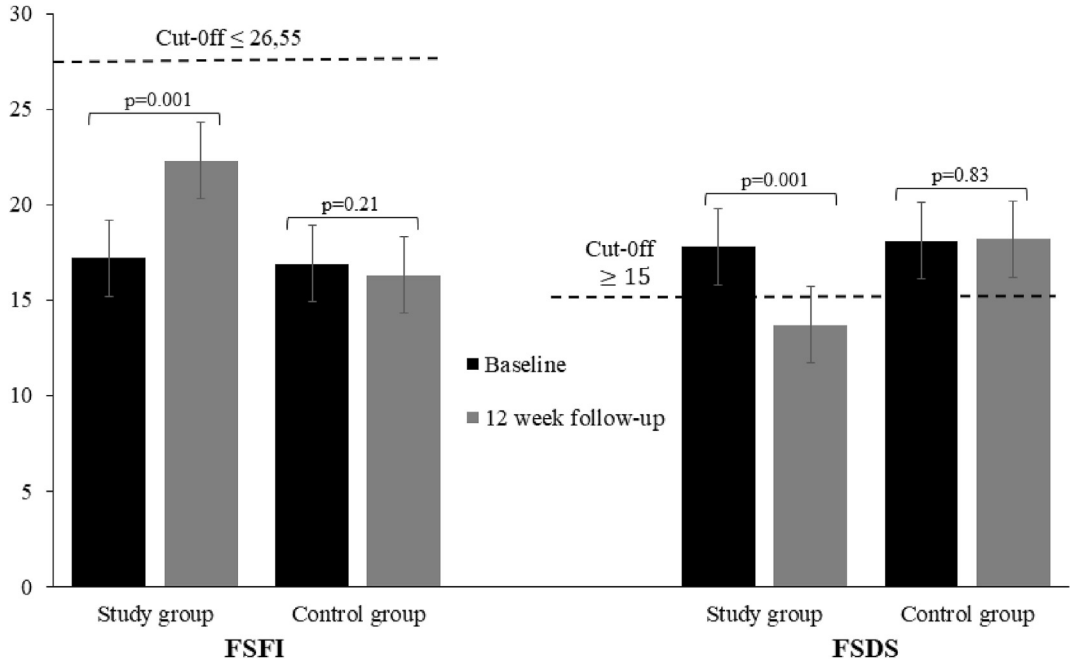

Fig. 3. Intragroup comparison of sexual function assessed by the female sexual function index (FSFI), and sexual distress level measured by the female sexual distress scale (FSDS) of postmenopausal women treated with hyaluronic acid (study group) or using on-demand lubricants or moisturizers (control group).

(having anti-inflammatory properties) could justify the benefits that women got from using the gel. All the benefits obtained by the women on treatment with HA/BG-1 vaginal gel were not found in the control group, in which the participants adopted an on-demand regimen of vaginal lubricants or moisturizers.

Some authors obtained similar results to ours with regard to VHI scores, and better VMI than us in women on 30-day [31] or 12-week vaginal HA administration [32]. However, we could not fully compare our results with those obtained by other authors as only HA vaginal administration was used in their studies. Anyway, in these studies the authors reported a moderate estrogenic stimulation index even after 30 days of treatment, meaning the HA had immediate effects on the vaginal epithelium, similar to estrogenic ones [31]. Moreover, it was not possible to compare our results to those obtained by some authors regarding FSFI and SF scores, as different analytical methods were used [31]. On the other hand, some authors investigated, by randomized studies, the effectiveness of a vaginal cream containing HA or conjugated estrogen, on symptoms of vaginal atrophy, and on VMI in postmenopausal women. They observed an improvement after 8 weeks of treatment. HA was found to be more effective than conjugated estrogen for dryness, VMI, and some scores of vaginal symptoms. The authors concluded that HA might be an appropriate alternative for those women with medical contraindications or negative experiences with using hormonal treatments [33]. Other authors, by a randomized study, compared the effects of estradiol vaginal tablets with HA vaginal tablets and observed that both treatments improved vaginal symptoms and VMI after 8 weeks of usage, but the improvements were greater in women on estrogen than on HA [34].

Table 4
Intragroup statistical analysis of sexual function investigated by the female sexual function index (FSFI).

FSFI Items	Baseline	12-week follow-up	*P*
	n.50	n.42	
Desire	2.9 ± 1.1	3.2 ± 1.3	p < 0.2
Arousal	2.7 ± 1.5	3.5 ± 1.2	p < 0.009
Lubrication	2.8 ± 1.2	4.5 ± 1.2	p < 0.0001
Orgasm	2.9 ± 1.5	3.4 ± 1.3	p < 0.1
Satisfaction	3.2 ± 1.3	3.9 ± 1.1	p < 0.009
Dyspareunia	2.7 ± 1.9	3.8 ± 1.8	p < 0.009

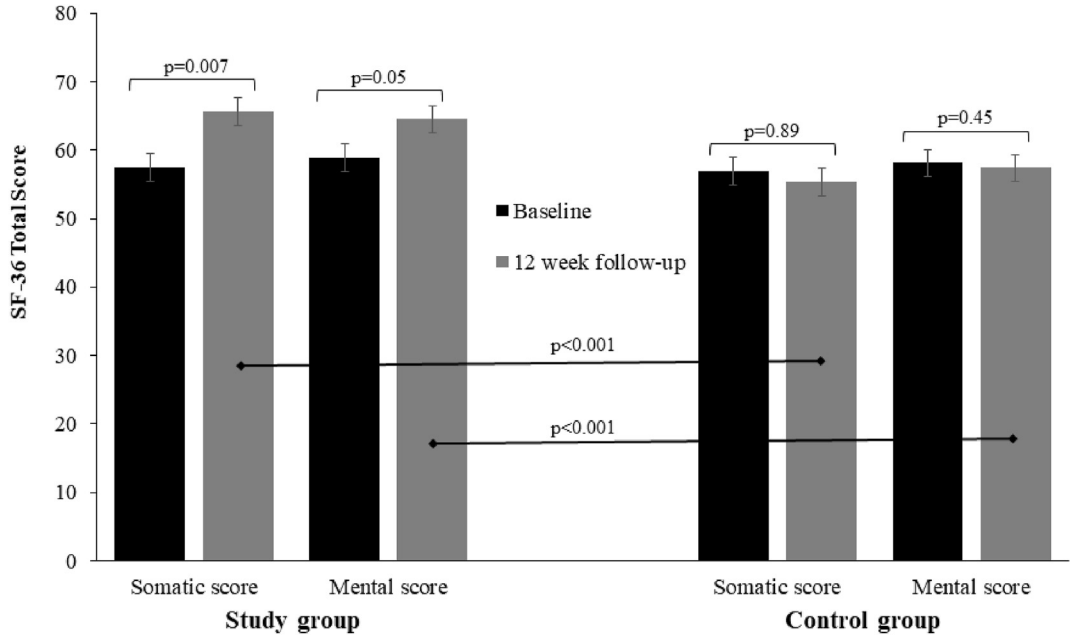

Fig. 4. Intragroup and intergroup comparison of the quality of life investigated by the SF-36 questionnaire of postmenopausal women treated with hyaluronic acid (study group) or using on-demand lubricants or moisturizers (control group).

In a more recent study, other authors reported similar results. In fact, they claimed that the symptoms of VVA improved in women either on estradiol vaginal or on HA, but the improvement of VMI was significantly higher in the hormonal group than in the non-hormonal group [35].

Finally, in a systematic review including five studies, the authors emphasized the lack of a consensus opinion [36]. In fact, three studies showed that despite the fact that HA was effective in improving the symptoms of vaginal atrophy, the difference between vaginal HA and vaginal estrogen was not statistically significant [37–39].

A limit of the current study —even if it could be evaluated as a mirror of real life -was to have considered an on-demand regimen in the control group. Consequently, we are not able to know what benefits women in the control group would have obtained using daily lubricants or moisturizers. This could be the aim of a future study. Moreover, the investigation of the effects of HA/BG-1 versus HA alone on postmenopausal women with VVA might be the aim of a further randomized study. At last, the use of the device in women with AVV secondary to breast cancer treatments should be studied.

Conclusions

Treatment with HA/BG-1 could be used in postmenopausal women who complain of vaginal dryness. The association of HA and BG-1 could synergistically improve the trophism and the inflammatory state of the vaginal epithelium. The amelioration of VVA-related signs could positively act on sexual function and QoL.

Ethics approval and consent to participate

Ethics Committee Catania 1, University Hospital Polyclinic, Catania, Italy, approved the study protocol. It conformed to the ethical guidelines of the 2013 Helsinki Declaration. Informed consent was obtained from all the study participants.

The research protocol was approved by the institutional review board of the Ethics Committee of the University Hospital Polyclinic, Catania, Italy, registered n. 84/2020/PO.

Declaration of competing interest

None.

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