European Review for Medical and Pharmacological Sciences 2019; 23: 6035-6044

A pilot study of soft gel technology: a new vaginal device to improve the symptomatology of vulvovaginal atrophy in post-partum, menopause and in patients with recurrent vulvovaginitis

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Abstract. – OBJECTIVE: This is a pilot study to evaluate the effectiveness of the treatment with Vaginal Soft gels technology in the improvement of common signs and symptoms in postmenopausal, postpartum and with recurrent vulvovaginitis patients. These conditions may cause the onset of Vulvovaginal Atrophy (VVA) with effects on sexual activity, self-confidence and daily activities. The main symptoms are itching, irritation and dryness. Many therapies have been evaluated and almost all those without hormonal component have shown poor results.

PATIENTS AND METHODS: Women diagnosed with severe VVA from January to September 2018 were recruited. The study groups were composed of 25 postmenopausal women, 30 post-partum women and 30 women with recurrent vulvovaginitis. For each group, patients were randomized 1:1 among those who carried out the experimental treatment and those that did not perform it. The efficacy of treatment was evaluated with a clinical visit in which Vaginal Health Index (VHI) was estimated. The symptomatology was determined through the questionnaire Female Sexual Function Index (FSFI).

RESULTS: A significant improvement has been shown with regard to the sexual function (orgasm, lubrification, pain) in patients who performed the treatment. A significant increase in VHI has been evaluated in postmenopausal patients (4 months p=0.054, 6 months p=0.005) and in recurrent vulvovaginitis but not in post-partum patients (4 months p=0.681, 6 months p=0.109).

An improvement of lubrication, satisfaction, orgasm, pain, as well as dyspareunia, was observed in the three study groups.

CONCLUSIONS: In this pilot study the treatment with soft gels seems to be effective in improving sexual health and atrophy being a treatment available for all types of patients thanks to the absence of systemic and local side effects. It is an excellent alternative especially for patients who cannot use hormones. These findings must be confirmed by larger and randomized further studies.

Key Words:
Vulvovaginal atrophy, Recurrent Vulvovaginitis, Postmenopausal atrophy, Postpartum atrophy.

Introduction

Vulvovaginal atrophy (VVA) is a little-known and underdiagnosed disorder that occurs in women between 30 and 50 years and it affects about one in two women in post-menopause.

Conditions that could predispose to the onset of VVA are hormonal modifications for example menopause or lacerations or vaginal surgery and also recurrent vulvovaginal infections. Indeed the post-partum laceration or alteration of cervicovaginal anatomy that follows some types of gynecological surgery, such as conization and/or trachelectomy predispose for VVA.

Generally, the VVA consists in a progressive modification of the vaginal and vulvar tissue structures as a consequence of the estrogens lack or anatomical, mechanical and inflammatory alterations, which lead to vaginal walls thinning so the tissue becomes less resistant and less, lubricated.

Therefore, VVA is characterized by the presence of a series of symptoms such as dyspareunia, vaginal and/or vulvar dryness and vaginal irritation and itching[1,2].

Unfortunately, VVA is a pathology still undervalued despite having very significant consequences on women's life's quality.

This condition also has very strong consequences on the couple's life, both on the relational point of view and on sexual intimacy. As many as 67% of women with VVA avoid intimacy with their partner[3-5].

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Especially for menopausal women, systemic hormone replacement therapy (HRT) or local vaginal estrogen therapy is currently available, which should be preferred when the systemic one is not necessary for other reasons. These treatments are supported by non-hormonal lubricants, that could be also evaluated in conditions not necessarily associated with the hormonal problem, although over 40% of women experience relief from symptoms considered insufficient[6].

Today the range of treatments to be used is wide enough also for women who cannot use estrogens, not even local: just think, for example, to alternative therapeutic solutions such as vaginal hyaluronic acid and vaginal laser or different creams that do not have the therapeutic impact of hormones. There are several possible therapeutic strategies with different results[7-10].

Furthermore, recently, a new oral drug, the non-estrogenic ospemifene was introduced (it is a SERM, selective estrogen receptor modulator), it has the potential to become the first alternative to local estrogens, especially for those conditions where hormone-based treatment is feared, such as women with breast cancer story or are completing the treatment cycle, and for all women who do not prefer local therapies[11].

Although, considering the great impact mostly of menopause on the quality of life[12], several therapeutic options are available. A series of surveys published about this topic have shown that the great majority of women are dissatisfied with the products available on the market to treat this condition, in both safety and efficacy terms and also regarding the administration methods[13-15].

In addition, another survey showed that although there are about 32 million the number of women suffering from VVA, especially related to menopause[16], only 7% of women use drugs to improve this condition[7,17]. Therefore, new options and therapeutic strategies are necessary and must be investigated. Vaginal Soft gels devices include a series of topical vaginal products, developed with the aim to treat the symptoms associated with vulvovaginal atrophy.

Soft gel Technology

Soft gel is a gel with a certain active ingredient associated with some excipients, contained within devices such as soft capsules, that can dissolve and release the product for oral absorption or by other body cavities mucosa (such as vaginal epithelium). They, generally, consist of a gelatin shell surrounding a filling liquid. The filling liquid is composed in this case by a mixture of different substances: ionic silver, Hyaluronic acid, Aloe Vera Extract, Mallow extract, Benzalkonium chloride.

The shells are a combination of gelatin, water, opaque and a plasticizer such as glycerin or sorbitol.

Soft gels are produced through a process known as encapsulation, using the rotary encapsulation process of the disk invented by Robert Pauli Scherer. The encapsulation process has been described as a form/fill/seal process. Two flat ribbons, consisting of the material constituting the shell, are produced on the machine and assembled on a double set of rotating molds. The molds contain grooves in the desired sizes and shapes, which cut the ribbons into a two-dimensional shape and form a seal on the outside.

At the same time, a pump delivers a precise dose of filling material through a nozzle built into a filling wedge, whose tip is located between the two strips between two dies at the cropping point. The wedge is heated to facilitate the sealing process. The wedge-shaped injection makes the two flat belts expand into the pockets of the molds, giving life to the finished three-dimensional product.

After encapsulation, the soft gel is dried from two days to two weeks, depending on the product.

The objective of this study is to evaluate the tolerability and efficacy of vaginal soft gel devices in 3 selected patient groups. The groups are: postpartum patients when lacerations or episiotomy occur, in recurrent vaginitis and in menopausal women. In these conditions, the majority of patients complain of the following various symptoms: vaginal dryness, dyspareunia, burning, itching, dysuria. Therefore, we can easily infer how the efficacy of these products could be indicated in these groups of patients. To date, products have been tested and tested, without constant and repeatable findings. The aim of our study is to increase the knowledge about the therapeutic use of soft gel for the treatment of VVA, especially in those clinical conditions predisposing more frequently to this disorder.

Collaterally, the timing for the efficacy achievement and an analysis of the benefits in the different groups of patients were evaluated, in order to determine what patients are candidates for treatment with Soft gels.

Patients and Methods

In the present study, patients who suffered from VVA were enrolled in the Gynecology UOC of the San Pietro Fatebenefratelli Hospital, Rome, from January 2018 to September 2018, for the following clinical conditions: postpartum (in case of lacerations or episiotomy), recurrent vulvovaginitis and menopause.

They had negative vaginal swabs for common germs, Chlamydia, Gardnerella, Mycoplasma, Trichomonas and gonococci, pap smear and mammogram (according to the patient's age) in the norm. At the time of enrollment of the study the patients underwent the following blood tests: CBC with leukocyte formula, HbsAg, HCV, HIV, TPHA, VDRL, Glycemia, PCR, AST, ALT, Bilirubin, Creatinine, Azotemia, Urine exam.

Inclusion criteria were VVA diagnosis caused by the above-listed clinical situations, age between 18 and 65 years old, ability to understand and, therefore, to be included in an experimental research protocol and compliance with treatment and control visits.

Exclusion criteria were abnormal Pap Test, vaginal swabs, mammography, positive pregnancy test, autoimmune or viral pathologies such as HIV, HCV, HBV and hormonal interventions in progress. Urinary and/or vaginal infections were treated before enrollment in the study. Being an innovative study, it was not possible to find a predefined statistical endpoint. For each group, the patients were randomized 1:1 between experimental treatment and no treatment. All patients were informed about the potential of participation in the experimental study. Therefore, they signed the informed consent about the inclusion in the study, the medical treatment and the personal data treatment. Study was approved by to the local Ethical Committee.

All patients at time 0 were visited to assess the loco-regional status and the baseline VVA level. The treatment consisted of Soft gel use. Patients underwent a check-up every 2 months. Treatment continued for at least 6 months or until tolerable by the patient. The efficacy of the treatment was evaluated on both the clinical visits, in which the Vaginal Health Index (VHI) was usually estimated, and on the questionnaires that patients reported at each check-up (every 2 months). VHI is an objective, score-based investigation tool, firstly elaborated and published by Bachmann and comprising of five vaginal parameters evaluated by clinical inspection: elasticity, fluid volume, pH, epithelial integrity and moisture. Each parameter is graded from 1 (worst condition) to 5 (best condition). The total score is between 5 and 25 and a score lower than 15 means vaginal atrophy[18].

A questionnaire was administered to each patient at time 0, 2.4 and 6 months: Female Sexual Function Index (FSFI).

The FSFI is a brief, reliable, multidimensional, self-report instrument for assessing sexual function during the past 4 weeks. The FSFI consists of 19 questions categorized into six domains of sexual function (desire, arousal, lubrication, orgasm, satisfaction, and pain). Scores for each FSFI domain were calculated by adding the scores for the individual domain questions and multiplying for the domain factor (0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm, satisfaction, and pain). Each FSFI domain is graded using a scale of 0 to 6, with the exception of the desired domain, which is graded on a scale of 1.2 to 6. The total FSFI score is defined as the sum of the individual domain scores and ranges from a minimum score of 2 to a maximum score of 36 points. Sexual dysfunction was defined as a total FSFI score no higher than 26.55 of a maximum possible score of 36[19-21]. All data were collected in a database and then statistically analyzed. The minimum follow-up was 6 months. Patients were divided into three groups: 30 post-partum patients, 30 patients with vulvovaginitis and 25 menopausal patients. In the menopausal group, 13 were treated with vaginal soft gel and 12 were not treated. In the postpartum group, 14 patients applied vaginal soft gel and 16 didn't perform it. In the last group, 14 out of 25 patients with recurrent vulvovaginitis used soft gel device.

Statistical Analysis

We have collected and analyzed questionnaires answers data of both treated and not treated patients. We have calculated the average of the results and the statistic Student's *t*-test was performed. The study groups were compared at a different moment of the study: at zero, four and six months of treatment. Results were considered statistically significant for p-value<=0,05 and for a confidence interval at 95%.

Results

From the statistical analysis of the data, it was observed a clinical overall improvement of vulvovaginal atrophy in patients treated with soft gel

devices. Results showed a recovery of sexuality thanks to the average increase in satisfaction and reduction of pain in treated patients. In menopausal and in post-partum patients, soft gel treatment improved orgasm. VHI index increased after six months of soft gel therapy in post-menopausal and with recurrent vulvovaginitis patients (Figure 4). Already after 4 months of soft gels therapy, postmenopausal patients showed resolution of dyspareunia (p=0.002) having benefit for sexuality also thanks to the non-significant trend of orgasm growth and the VHI increase (Figure 1). At six months of therapy, however, there was a clear and significant improvement of VHI (13.46 *vs.* 15.25), lubrication (p= 0.010), satisfaction (p= 0.001) as well as dyspareunia and orgasm (Table I).

In the post-partum group, 14 patients who performed soft gel therapy had benefit in term of satisfaction (p= 0.001), pain (p= 0.010) and orgasm (p= 0.023), after 4 months of treatment. At the end of the six months of therapy, there was a significant effect of soft gels also on lubrication (p= 0.002) and arousal (p= 0.009) (Table II). Although VHI incremented, it did not have a significant increase (Figure 2).

The last patients group evaluated is those with recurrent vulvovaginitis with negative pads, but they presented an alteration of tissues and vulvovaginal mucous membranes. In this group, 14 patients carried out treatment with soft gels and 14 didn't perform the treatment. It was observed that longer therapy was more effective (Figure 3). In these patients, there was a significant improvement of the VHI even after 4 months of treatment that was confirmed at 6 months, in association with lubrication, satisfaction and pain well-being (Table III).

Soft gels treatment with soft didn't show any effect on the increase of desire in none of the study groups.

Discussion

VVA is an important contributor to the female sexual disorders and the reduction of quality of life. All VVA symptoms impact on woman daily living[6].

The impact of VVA is not well recognized by patients, they consider it as a consequence of age or recurrent infections. It is important for gynecologist to investigate patient symptoms e sexual health because this type of disorder is often underestimated despite having a significant negative impact on a woman's quality of life[21-23].

In menopause, the most proposed therapy today is HRT but many patients refused it because of the hormonal systemic effects or contraindication in particular conditions. There isn't yet a well-defined position on HRT therapy in women with breast, ovarian and endometrial cancer, so the evaluation of the risk of hormonal treatment may be estimated with the oncologist[24]. Non-hormonal therapy as moisturizers or lubricants improves dryness and burning but only transitory and patients are not very compliant for a long time.

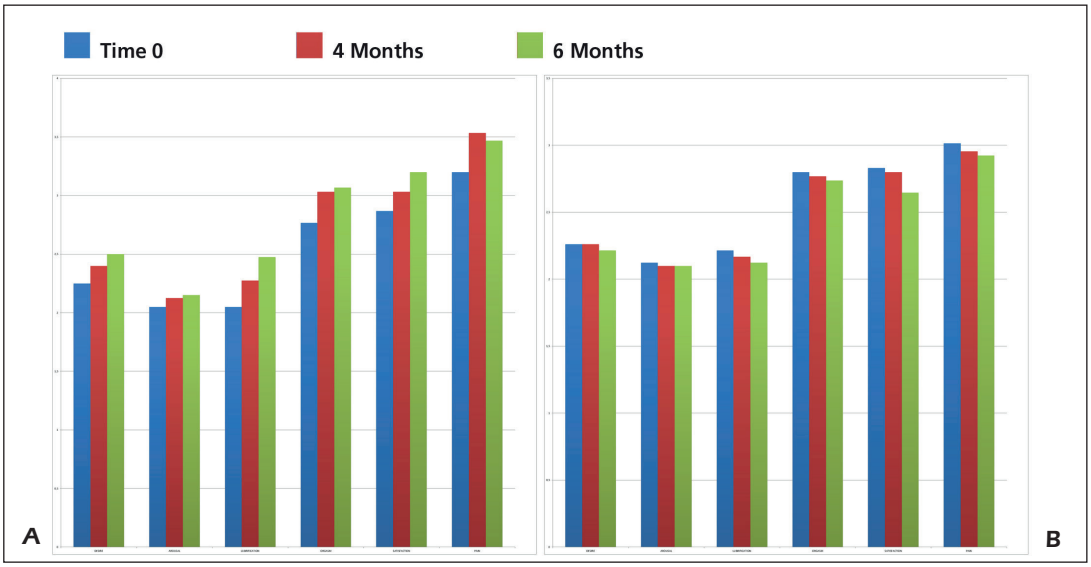

Figure 1. A, Menopausal patients with soft-gel therapy. **B**, Menopausal patients without soft-gel therapy.

Table I. Soft gel effect on menopausal patients at time 0; 4 months; 6 months.

	MENOPAUSAL PATIENTS			
	Therapy	**N**	**Mean ± DS**	***p*-value**
TIME 0				
Desire	yes	12	2.250 ± 0.5792	0.966
	no	13	2.262 ± 0.7411	
Arousal	yes	12	2.050 ± 0.3580	0.643
	no	13	2.123 ± 0.4146	
Lubrification	yes	12	2.050 ± 0.4400	0.354
	no	13	2.215 ± 0.4337	
Orgasm	yes	12	2.767 ± 0.3601	0.837
	no	13	2.800 ± 0.4320	
Satisfaction	yes	12	2.867 ± 0.3339	0.823
	no	13	2.831 ± 0.4461	
Pain	yes	12	3.200 ± 0.3814	0.317
	no	13	3.015 ± 0.5064	
VHI	yes	12	13.50 ± 1.624	0.650
	no	13	13.77 ± 1.301	
4 MONTHS				
Desire	yes	12	2.400 ± 0.5117	0.966
	no	13	2.262 ± 0.6995	
Arousal	yes	12	2.125 ± 0.3720	0.643
	no	13	2.100 ± 0.3873	
Lubrification	yes	12	2.275 ± 0.4330	0.354
	no	13	2.169 ± 0.3038	
Orgasm	yes	12	3.033 ± 0.2674	0.837
	no	13	2.769 ± 0.3816	
Satisfaction	yes	12	3.033 ± 0.2674	0.823
	no	13	2.800 ± 0.4619	
Pain	yes	12	3.533 ± 0.2309	0.317
	no	13	2.954 ± 0.5301	
VHI	yes	12	14.50 ± 1.168	0.650
	no	13	13.54 ± 1.198	
6 MONTHS				
Desire	yes	12	2.500 ± 0.5625	0.199
	no	13	2.215 ± 0.5129	
Arousal	yes	12	2.150 ± 0.3580	0.741
	no	13	2.100 ± 0.3873	
Lubrification	yes	12	2.475 ± 0.3646	0.010
	no	13	2.123 ± 0.2587	
Orgasm	yes	12	3.067 ± 0.2605	0.023
	no	13	2.738 ± 0.3948	
Satisfaction	yes	12	3.200 ± 0.2954	0.001
	no	13	2.646 ± 0.4176	
Pain	yes	12	3.467 ± 0.1969	0.001
	no	13	2.923 ± 0.4438	
VHI	yes	12	15.25 ± 1.815	0.005
	no	13	13.46 ± 0.967	

In postpartum period, vulvovaginal ecosystem is subjected to change due to both estrogenic deprivation and mechanical alterations of childbirth. It is known that these patients complain dyspareunia, vaginal dryness and deterioration of vulvovaginal tissues[25]. Same symptoms are typical of women who suffer from recurrent infections that lead to vaginal microsystem and alter mucosa and vulvovaginal architectural[26]. These conditions degrade sexual health of the woman.

Table II. Soft gel effect on postpartum patients at time 0; 4 months; 6 months.

	POSTPARTUM PATIENTS			
	Therapy	**N**	**Mean ± DS**	***p*-value**
TIME 0				
Desire	Yes	14	1.757 ± 0.5983	0.403
	No	16	1.950 ± 0.6387	
Arousal	Yes	14	2.357 ± 0.2848	0.597
	No	16	2.288 ± 0.4080	
Lubrification	Yes	14	2.229 ± 0.2813	0.348
	No	16	2.344 ± 0.3669	
Orgasm	Yes	14	1.857 ± 0.3715	0.901
	No	16	1.875 ± 0.4058	
Satisfaction	Yes	14	1.714 ± 0.3302	0.428
	No	16	1.825 ± 0.4123	
Pain	Yes	14	2.086 ± 0.6871	0.954
	No	16	2.100 ± 0.6613	
VHI	Yes	14	16.29 ± 1.729	0.527
	No	16	15.94 ± 1.237	
4 MONTHS				
Desire	Yes	14	3.129 ± 0.5355	0.441
	No	13	2.954 ± 0.6226	
Arousal	Yes	14	3.150 ± 0.2565	0.051
	No	13	2.954 ± 0.2402	
Lubrification	Yes	14	2.936 ± 0.2678	0.967
	No	13	2.931 ± 0.3497	
Orgasm	Yes	14	2.886 ± 0.4204	0.023
	No	16	2.500 ± 0.4502	
Satisfaction	Yes	14	2.857 ± 0.3797	0.001
	No	16	2.325 ± 0.3642	
Pain	Yes	14	3.314 ± 0.59	0.010
	No	16	2.77 ± 0.47	
VHI	Yes	14	17.71 ± 0.914	0.681
	No	13	17.54 ± 1.266	
6 MONTHS				
Desire	Yes	14	3.257 ± 0.5110	0.976
	No	16	3.263 ± 0.4365	
Arousal	Yes	14	3.407 ± 0.4009	0.009
	No	16	3.075 ± 0.2324	
Lubrification	Yes	14	3.536 ± 0.4877	0.002
	No	16	3.000 ± 0.3633	
Orgasm	Yes	14	3.657 ± 0.3081	0.000
	No	16	2.825 ± 0.3715	
Satisfaction	Yes	14	3.257 ± 0.4926	0.000
	No	16	2.500 ± 0.3724	
Pain	yes	14	3.542 ± 0.4925	0.004
	no	16	3.050 ± 0.3540	
VHI	yes	14	18.57 ± 1.284	0.109
	no	16	17.81 ± 1.223	

Most of the scientific papers have evaluated the benefits of estrogen substances in the treatment of sexual disorders, but instead, no study has evaluated the benefits of using these soft gel devices[21-23].

Soft gel device in sexual and gynecological disorders could be an alternative therapy with benefits for VVA symptoms for all type of patients thanks to the absence of adverse effects.

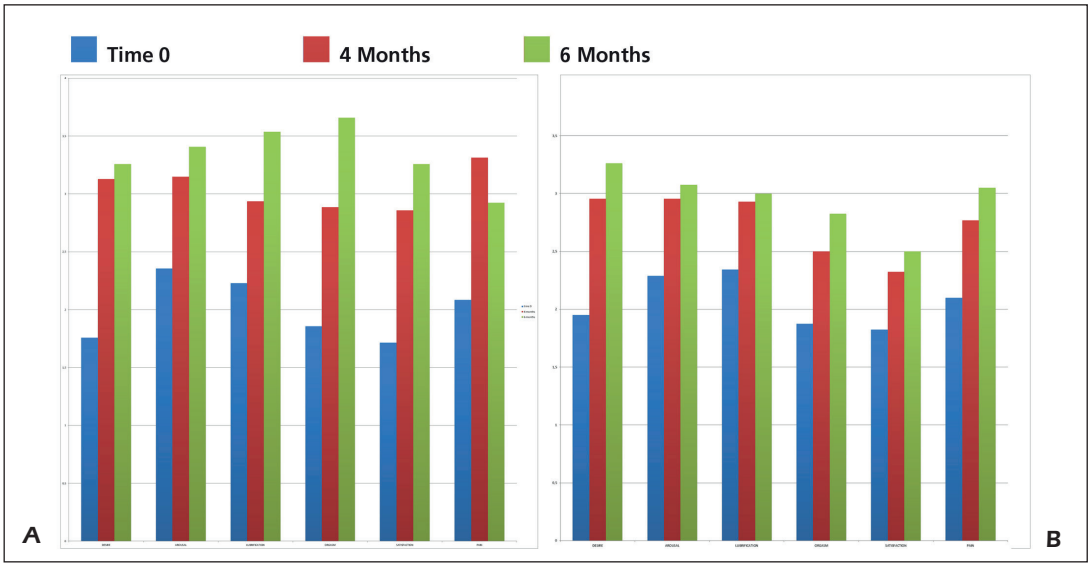

Figure 2. A, Postpartum patients with soft-gel therapy. **B**, Postpartum patients without soft-gel therapy.

In this pilot study, a significant clinical improvement of symptoms was observed in all patients treated with soft gel, already after four months, compared with the absence of treatment. Because of the small number of patients and the short observation period, only few parameters were statistically significant.

Best results were observed after a longer period of soft gels use and symptoms improvement increased proportionally to the time of administration.

Soft gels have the advantage of being able to significantly improve the quality of life even in menopausal patients who cannot resort to the use of estrogens for oncological risk, as well as improving and speeding up recovery and outcome in postpartum patients and in women with infectious diseases.

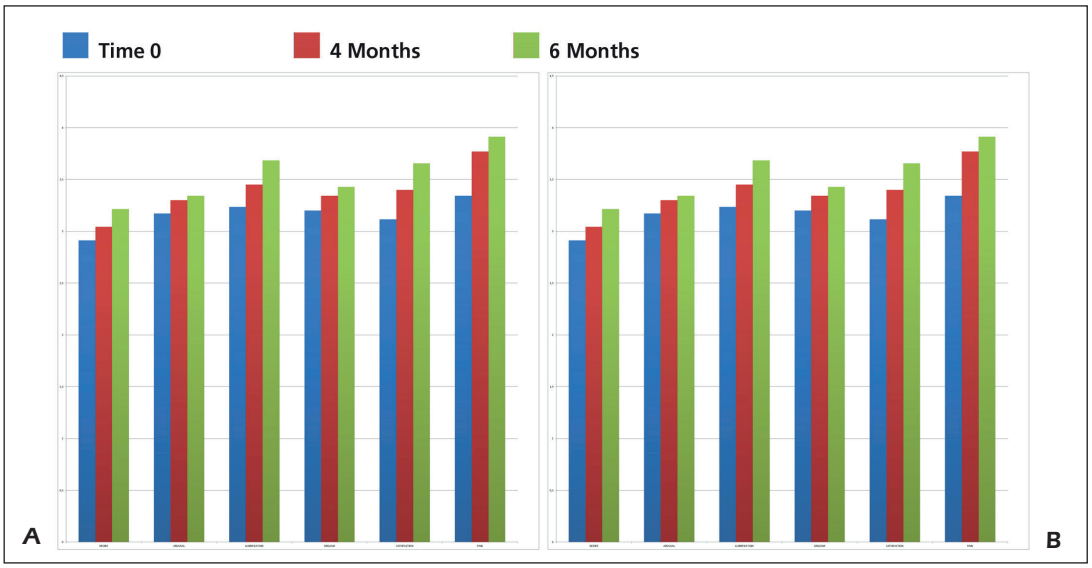

Figure 3. A, Patients with vulvovaginitis with soft-gel therapy. **B**, Patients with vulvovaginitis without soft-gel therapy.

Table III. Soft gel effect on patients with recurrent vulvovaginitis at time 0; 4 months; 6 months.

	RECURRENT VULVO VAGINITIS			
	Therapy	N	Mean ± DS	*p*-value
TIME 0				
Desire	Yes	14	2.914 ± 0.8104	0.348
	No	14	3.171 ± 0.5967	
Arousal	Yes	14	3.171 ± 0.6305	0.714
	No	14	3.086 ± 0.5934	
Lubrification	Yes	14	3.236 ± 0.4272	0.805
	No	14	3.193 ± 0.4795	
Orgasm	Yes	14	3.200 ± 0.4438	0.616
	No	14	3.286 ± 0.4487	
Satisfaction	Yes	14	3.114 ± 0.2797	0.137
	No	14	3.314 ± 0.3978	
Pain	Yes	14	3.342 ± 0.4032	0.133
	No	14	3.600 ± 0.4706	
VHI	Yes	14	16.43 ± 1.399	0.196
	No	14	16.87 ± 1.383	
4 MONTHS				
Desire	Yes	14	3.450 ± 0.4519	0.059
	No	14	3.107 ± 0.4649	
Arousal	Yes	14	3.343 ± 0.3715	0.717
	No	14	3.286 ± 0.4487	
Lubrification	Yes	14	3.400 ± 0.3038	0.234
	No	14	3.229 ± 0.4286	
Orgasm	Yes	14	3.771 ± 0.2054	0.066
	No	14	3.571 ± 0.3315	
Satisfaction	Yes	14	17.86 ± 1.099	0.050
	No	14	17.00 ± 1.109	
Pain	Yes	14	3.450 ± 0.4519	0.059
	No	14	3.107 ± 0.4649	
VHI	Yes	14	3.343 ± 0.3715	0.717
	No	14	3.286 ± 0.4487	
6 MONTHS				
Desire	Yes	14	3.214 ± 0.6049	0.109
	No	14	2.871 ± 0.4811	
Arousal	Yes	14	3.343 ± 0.4536	0.092
	No	14	3.043 ± 0.4536	
Lubrification	Yes	14	3.686 ± 0.4622	0.001
	No	14	3.043 ± 0.4536	
Orgasm	Yes	14	3.429 ± 0.3024	0.240
	No	14	3.257 ± 0.4398	
Satisfaction	Yes	14	3.657 ± 0.3797	0.000
	No	14	3.114 ± 0.3207	
Pain	Yes	14	3.914 ± 0.703	0.000
	No	14	3.514 ± 0.2797	
VHI	Yes	14	18.07 ± 1.072	0.016
	No	14	16.93 ± 1.269	

Conclusions

This is a pilot study that shows as soft gel device could be a valid treatment for VVA with therapeutic effects and well accepted by patients.

The advantage of these devices is the absence of adverse effects and the possibility of using them for long periods, with a consistent improvement of symptomatology and women's quality of life. These results are certainly preliminary

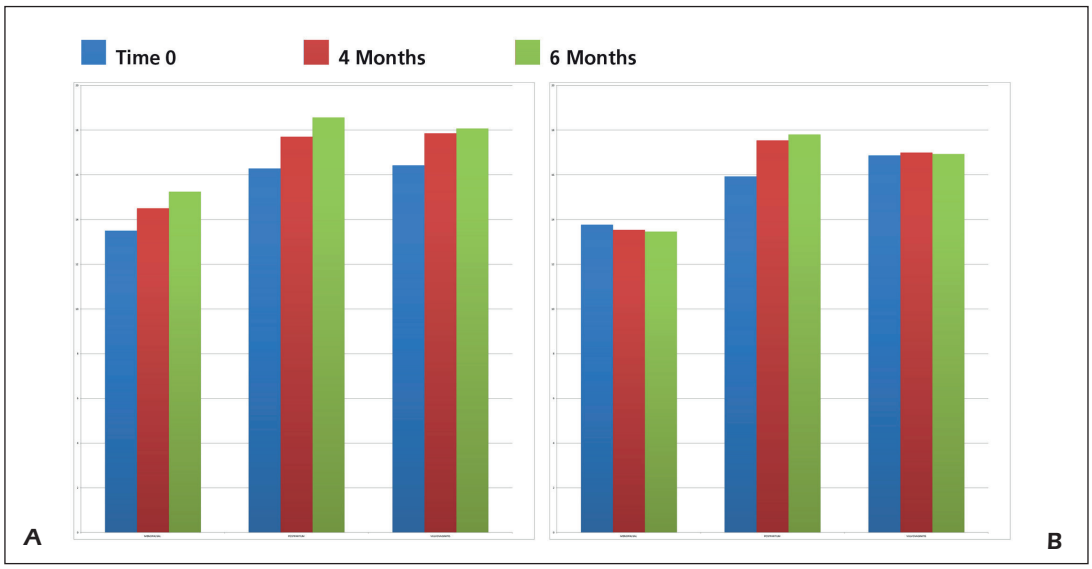

Figure 4. A, VHL in different groups with soft-gel therapy. **B**, VHL in different groups without soft-gel therapy.

and need to be followed by further larger trials to support these data, to study other benefits and advantages of soft gels device treatment, and to define the modality and times necessary to obtain the best outcome on women's health.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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