Low-molecular weight hyaluronic acid for the treatment of vulvovaginal atrophy: an innovative clinical practice

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ABSTRACT — OBJECTIVE: *Vulvovaginal Atrophy / Genitourinary Syndrome of Menopause (VVA/GSM) is a clinical manifestation of symptoms at vaginal level, associated to menopause, as dryness, burning, and itching, or impairment of sexual life. Physicians have several options that can be adopted to improve patient health. The clinical use of Low Molecular Weight Hyaluronic Acid (LMWHA) represents one of the most interesting approach for these patients. The aim of this work is to evaluate the ability of LMWHA to improve VVA/GSM symptoms on menopausal women.*

PATIENTS AND METHODS: 50 menopausal women reporting dryness, itching, burning and dyspareunia, were enrolled. Vaginal and oral administrations of LMWHA were performed in association with radiofrequency (RF) and poration (PO) treatment sessions. For the first five weeks, one oral tablet with 100 mg of LMWHA was administered everyday while, at vaginal level, one suppository for day, containing 5 mg of LMWHA, 1 mg of Vitamin A and 1 mg of Vitamin E, was administered in the two days preceding RF. One RF/PO session for week was performed, during the first five weeks. When RF was interrupted, LMWHA treatment was continued with daily administrations of one suppository for two weeks and one tablet for ten months. At baseline (T0), and after 5 weeks (T1), 6 months (T2) and 12 months (T3) all patients have reported symptoms perception. Primary and secondary outcomes of this study were improvements of vaginal dryness and of all other symptoms respectively.

RESULTS: A rapid improvement of vaginal dryness was reported when compared to T0, with reductions of 80.28%, 79.77% and 67.91% at T1, T2 and T3, respectively. In a similar way, also all other symptoms were resulted improved, and the result has remained stable over time.

CONCLUSIONS: Considering data obtained, LMWHA administration represents an innovative solution to improve symptomatology of VVA/GSM patients.

KEYWORDS
Low-Molecular Weight Hyaluronic Acid, Quality of Life, Vulvovaginal Atrophy, Radiofrequency, Genitourinary Syndrome of Menopause.

INTRODUCTION

Childbirth, hormonal changes, aging, are responsible of typical modifications of female reproductive system, favouring the onset of clinical symptoms, as vaginal laxity, stress urinary incontinence or loss of vaginal lubrication, and impairing their quality of life (QoL)[1,2]. Particularly, when menopause occurs, the onset of a condition known as vulvovaginal atrophy (VVA) is

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very common[1,3,4]. VVA is a chronic status caused by an alteration of oestrogen levels that is reflected on vaginal vessels, collagen synthesis and on vaginal epithelium leading to a progressive reduction of tissue vascularization, mucosal dryness, reduced vaginal elasticity, increased mucosa fragility, and reduced epithelium maturation[3,4]. VVA is characterized by several clinical signs and symptoms as increase of pH, pallor, thinning, vaginal dryness, dyspareunia, itching, burning, and recurrent vaginal infections. Recently a more inclusive and more user-friendly description was developed about genitourinary tract symptoms related to menopause known as Genitourinary Syndrome of Menopause (GSM). The main consequence of this condition, initially, is dyspareunia, causing the decrease of intimate relationships[3]. In this way, VVA/GSM has repercussions on relationship with partner and family, reducing woman's self-esteem and contributing to decrease her QoL. In a study by Palma et al[5] on nine hundred thirteen postmenopausal females (average age 59.3 ± 7.4 years), VVA/GSM were diagnosed on 722 women, corresponding to 79.1%, with a prevalence ranging from 64.7% to 84.2%, starting from 1 to 6 years after menopause. This is useful understand the huge impact of this condition on women health. Nowadays, physicians can adopt several options to improve VVA/GSM symptoms[6,7]: hormonal therapies (as oestrogen or oxytocin), hormonal receptor modulators (as Ospemifen)[8-10] physical treatments (as CO_2, Erbium lasers or Radiofrequency)[11-13], or Non-hormonal treatments (as Vitamins D and E, vaginal dilators, probiotics or hyaluronic acid)[7,14-16]. Thanks to its immunoregulatory and re-hydrating activities, the clinical use of hyaluronic acid (HA) represents one of the most interesting approach to help patients with VVA/GSM. HA is a mucopolysaccharide, naturally present in all organisms, consisting of a linear polyanion of 3-D-glucuronic acid and D-N-acetylglucosamine units linked with alternating β-1,4 and β-1,3 glycosidic bonds. A completed hyaluronan molecule can be composed by a huge number of repeated disaccharides (as 10.000 or more repetitions) and a molecular mass of 4 million Dalton (Da). Its simple structure is strongly conserved throughout all mammals, showing the importance of HA. In the body, HA is present in high quantity as hyaluronate, its salt form, particularly in soft connective tissues and represents the principal glycosaminoglycan in the body fluids such as synovial fluid or vitreous humour[17,18]. HA is fundamental for elastoviscosity maintenance of connective tissues, hydration, proteoglycans synthesis in extracellular matrix and, moreover, participates in some important pathways as cell detachment, mitosis, migration, and inflammation[19]. Beyond its important physiological role, the real limit of HA treatment is its administration. Indeed, due to its high molecular mass, this substance is not well absorbed when applied to the skin or mucosa, forming a thin, light permeable, invisible, viscoelastic surface film[20]. To overcome this limit, an interesting opportunity seems to be represented by HA with low molecular weight. Low-Molecular Weight Hyaluronic Acid (LMWHA), thanks to its properties, can be more easily absorbed, interacting with several cells involved in proliferation processes[21] and immunity system as osteoclasts, dendritic cells and macrophages[22-25]. In this regard, in several studies LMWHA has shown anti-inflammatory properties useful to counteract gynaecological side effects due to radiation therapy[18,26-28]. Another innovative treatment increasingly used to treat women with VVA/GSM is a thermal treatment with a low-energy radiofrequency (RF) device that have shown interesting data[29-33]. This technology leverages the endogenous heat due to molecular motion of charged particles induced by the application of an electrical field on tissue treated[34-36]. RF devices that can be unipolar, monopolar, bipolar, or multipolar, induce tissue temperatures between 40 to 45°C and this activates fibroblasts to produce collagen through heat shock protein[37]. Several studies with this technology have shown interesting effects on skin laxity, mechanical strength of skin, neo-collagenesis and elastogenesis[36]. For all these reasons, the aim of this work is to evaluate the effect of LMWHA and RF on VVA/GSM symptoms in menopausal women. Particularly, considering the renowned hydrating properties of LMWHA[26,38], the main aim of this study is an improvement of vaginal dryness. Improvements of burning, itching and dyspareunia were also evaluated.

PATIENTS AND METHODS

Study population and treatments

Menopausal women aged 40-70 years old and afferent from October 2018 to March 2019 to the Department of Maternal, Infantile, Obstetrics and Gynaecology of Melegnano Hospital for vaginal rejuvenation, reporting dryness, itching, burning and dyspareunia, at vaginal level were enrolled. Inclusion criteria of this pilot study were considered: a diagnosis of menopause from at least 1 year, moderate or severe vaginal atrophy, presence of one or more symptoms among itching, burning and dyspareunia and negative pap test and mammography. Instead, genital abnormalities, vaginal infections in the last two months, positive pap test, hormonal replacement therapy, vaginal treatments, involvement in other clinical studies and diagnosis of Sjogren syndrome were considered exclusion criteria. LMWHA was administered to all women enrolled combining vaginal (Santes® vaginal suppository, Lo.Li. Pharma, Rome, Italy) and oral (Ialos®, Lo.Li. Pharma, Rome, Italy) administrations. For the first five weeks, one oral tablet with 100 mg of LMWHA was administered everyday while, at vaginal level, one suppository for day,

containing 5 mg of LMWHA, 1 mg of Vitamin A and 1 mg of Vitamin E, was administered in the two days preceding RF. Particularly, vaginal suppository in the RF day was administered just before the treatment in association with poration (PO), a delivery system that induces a transitory increase of permeability by the application of an electrical impulse, favouring an improved LMWHA absorption at vaginal level.

The RF/PO treatment was performed once a week for 5 consecutive weeks. The duration of every RF/PO treatment session was 20 minutes, of which 10 minutes for RF, at a frequency treatment of 1 MHz, and 10 minutes for PO. After the first five weeks of treatment, RF was interrupted and LMWHA treatment was continued combining oral and vaginal administrations for further two weeks, with one suppository and one tablet every day. Finally, only one tablet for day was administered to all women as maintenance therapy for the following ten months. After these months, all patients were subjected to a follow-up period of 2 months. At every timepoint, all patients have also reported their symptoms perception, classifying vaginal dryness on a Visual Analogue Scale (VAS) and dyspareunia, burning and itching as absent, mild, moderate or severe. Moreover, patient's health was evaluated by gynaecological examination and subjective evaluation of symptoms. Particularly, pap-test and transvaginal echography were performed to all patients at baseline (T0), after the completion of RF/PO sessions (T1), after 6 months (T2) and after 12 months (T3). Considering the renowned hydrating properties of LMWHA, primary outcome of this study is the improvement of vaginal dryness. Improvements of burning, itching and dyspareunia were considered secondary outcomes. All subjects involved provided written Informed Consent Form before participation. The study was conducted following the Ethical principles of the Declaration of Helsinki and the national laws.

Statistical analysis

A statistical analysis of data obtained was performed to confirm the efficacy of this treatment. Sample size was calculated supposing a significant improvement of vaginal dryness at least in 50% of patients at the end of treatment, with 90% of power ($\alpha = 0.05$), and a maximum of 10% dropout, considering the vaginal dryness improvement reported in other papers with LMWHA treatments[26,39,40] and frequency of this symptom in the population[3]. The repeated measure ANOVA was applied to compare the mean scores of symptoms evaluated (dyspareunia, itching, burning and dryness) before treatment and at the three timepoints. The level of significance was set at $p<0.05$ for all the tests. All statistical analyses were performed using OpenEpi - Open Source Epidemiologic Statistics for Public Statistical Software - Version 3.01.

RESULTS

For this pilot study, fifty menopausal women, with an average age of 55.03 ± 6.81 years, reporting dryness, dyspareunia, itching and burning, have completed all treatments. Baseline characteristics of study population are summarized in Table 1. Vaginal dryness was strongly perceived by patients as confirmed by an average score of 7.74 recorded by VAS (Table 1). Moreover, most patients have reported, at T0, a severe degree for all symptoms, with percentages ranging between 34% of patients with itching and 78% of cases of dyspareunia. All patients have shown a rapid improvement of their symptoms. A reduction of 80.23% of vaginal dryness was reported at T1 thanks to the combined use of LMWHA in association with RF/PO treatments, as shown in Figure 1. This result was remained stable over time, with a vaginal dryness reduction of 79.80 % at T2. At T3, two months after LMWHA treatment interruption, the improvement of vaginal dryness slightly worsened, with a reduction of 67.93%. Similar results were achieved also with dyspareunia, burning and itching as reported in Figure 2. Particularly, at T1, T2 and T3 no patient has reported a severe degree of dyspareunia, burning or itching, with the 64% patients that have reported absence of symptoms at T1. Also, for these symptoms, the improvements remained stable at T2 and then got slightly worse at T3. In regard with burning, the percentage of patients with moderate or severe degrees, that at T0 was about the 88%, was reduced to the 2% at T1 and then remained stable at T2 and T3. On the contrary, the percentage of cases with absence or mild degree of burning was increased from 12% at T0 to 98% at T1, remaining stable also at T2 and T3. However, at T3, the number of cases with absence of burning was reduced passing from 64% to 48% while the number of patients with a mild degree was increased from 34% to 50%.

Table I. Baseline characteristics of patients involved.

BASELINE PATIENTS DATA				
Patients evaluated (N)	50			
Average Age (years ± SD)	55.03 ± 6.81			
Dryness (VAS scale ± SD)	7.74 ± 1.35			
Symptoms evaluation	A	Mi	Mo	S
Dyspareunia (%)	0	4	18	78
Burning (%)	0	12	36	52
Itching (%)	0	32	34	34

In this table is reported the number of patients (N) enrolled and the average age ± standard deviation (SD) of these. Moreover, vaginal dryness perception by patients on Visual Analogue Scale (VAS) 1-10 at baseline is reported. Finally, the distribution (%) of patients' perception about burning, itching and dyspareunia degree (A: Absent; Mi: Mild; Mo: Moderate S: Severe) at baseline is reported.

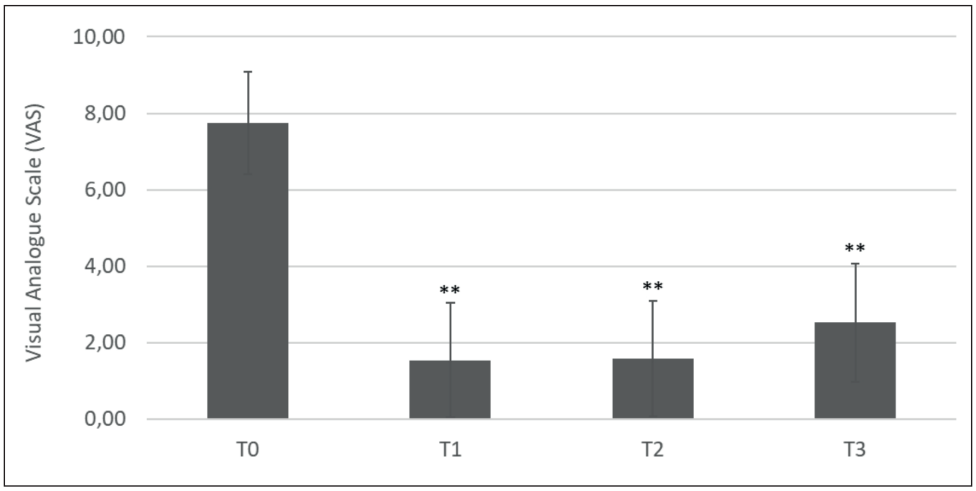

Figure 1. Evaluation of vaginal dryness at four time points on Visual Analogue Scale (VAS) before and after administration of Low-Molecular Weight Hyaluronic Acid and Radiofrequency (RF) / Poration (PO) treatments. Vaginal dryness perception by patients on Visual Analogue Scale (VAS) 1-10 at four time points (T0: Baseline; T1: Completion of RF/PO sessions - 5 weeks of starting treatment; T2: Maintenance therapy - 6 months of starting treatment; T3: Follow-up - 12 months of starting treatment). Statistical analysis was performed comparing T0 with T1, T2 and T3, using OpenEpi - Open Source Epidemiologic Statistics for Public Statistical Software - Version 3.01. **Significance was $p<0.001$.

This confirms the exacerbation of symptoms at T3. In a similar way, a reduction of cases with moderate or severe degrees of itching was reported, from 68% to 0% reported at T1, T2 and T3, corresponding to an increase of patients with absence or mild degrees from 32% to 100% at T1, stably maintained also at T2 and T3. Finally, also dyspareunia was strongly improved, with a reduction of cases with moderate or severe degree from 96% at T0 to 2% at T1 and T2, and then increased to 8% at T3. This reduction has been counterbalanced by an increase of cases with absence or mild degrees of dyspareunia from 4% at T0 to 98% at T1 and T2 which was followed by a slight worsening to 92%.

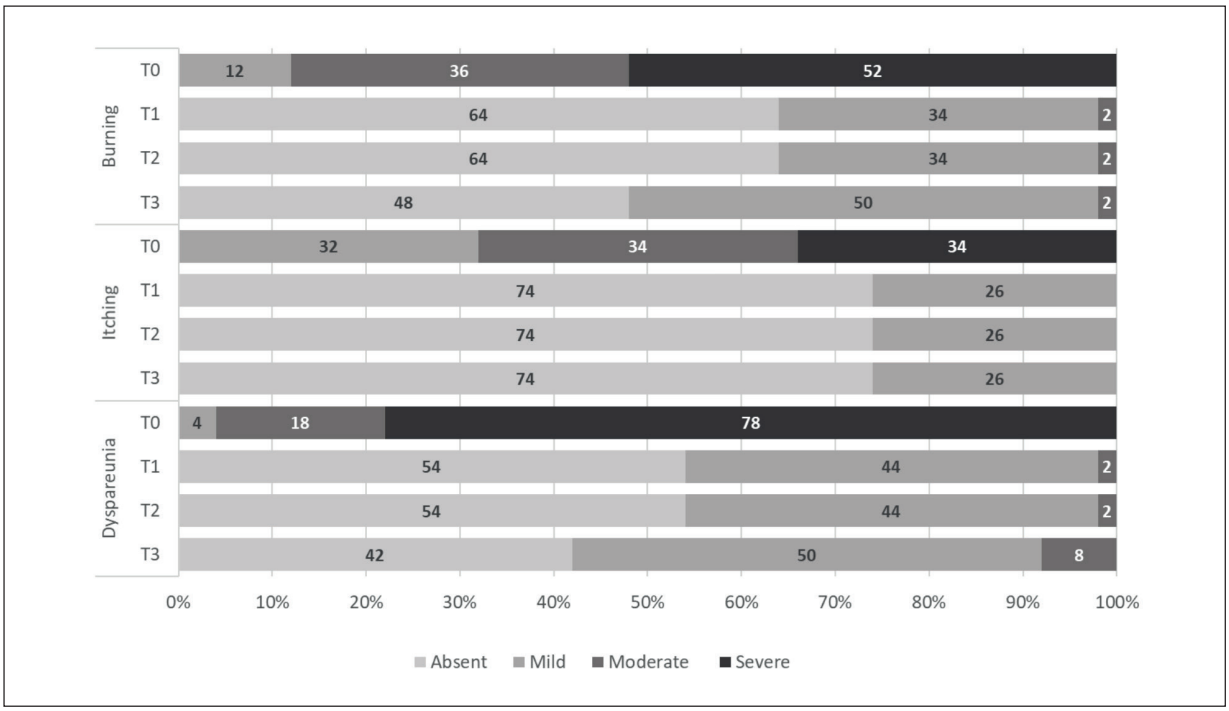

Figure 2. Percentage distribution of burning, itching and dyspareunia perception at four time points, before and after administration of Low-Molecular Weight Hyaluronic Acid and Radiofrequency (RF) / Poration (PO) treatments. The distribution (%) of patients' perception about burning, itching and dyspareunia degree (absent, mild, moderate or severe) at four time points (T0: Baseline; T1: Completion of RF/PO sessions - 5 weeks of starting treatment; T2: Maintenance therapy - 6 months of starting treatment; T3: Follow-up - 12 months of starting treatment). Statistical analysis was performed using OpenEpi - Open Source Epidemiologic Statistics for Public Statistical Software - Version 3.01. Significance was $p<0.001$

DISCUSSION

Vulvovaginal Atrophy/Genitourinary Syndrome of Menopause (VVA/GSM) is a definition that represents clinical manifestation of symptoms developed at genitourinary tract, associated to menopause and to the consequent oestrogen deficiency, as physical changes of vulva and vagina, urinary symptoms, impairment of sexual life and perception of vaginal burning, dryness and itching[3,5,41]. This condition is strongly prevalent in women aged 40 years or over, impacting strongly on relationship with partner and family, reducing woman's self-esteem and contributing to decrease the QoL[5]. In this regard, physicians have several options that can be adopted to improve patient health: hormonal therapies, physical treatments or nonhormonal treatments[7]. Thanks to its immunoregulatory and re-hydrating activities, the clinical use of HA represents one of the most interesting approach to help patients with VVA/GSM[7]. On this topic, in several studies LMWHA, thanks to its properties, resulted more easily absorbed, interacting with cells involved in proliferation processes and immunity system and favouring a better improvement of vaginal symptoms[18,26-28]. Considering data available on this topic, the administration of LMWHA on menopausal women with diagnosis of VVA/GSM, is not a surprise but its concomitant use with RF/PO represents, undoubtedly an interesting innovation for these patients. RF devices leverage the endogenous heat due to molecular motion of charged particles induced by the application of an electrical field on tissue treated[34-36]. Thanks to this technology, tissue temperatures between 40 to 45°C can be reached activating collagen production by fibroblasts[37]. Several studies with RF have shown interesting effects on skin laxity, mechanical strength of skin, neocollagenesis and elastogenesis[36]. For all these reasons, the simultaneous application with LMWHA can represent a turning point for these women and for their QoL. Moreover, LMWHA vaginal administration during RF/PO sessions could be a further improvement for this protocol, considering its increased absorption by vaginal mucosa. As previously reported, all these hypotheses were followed by interesting data that confirm the efficacy of this treatment clearly. The improvements about vaginal dryness, burning and itching were resulted important and stable over time confirming protocol potential. Moreover, the improvements obtained have induced a better QoL, counteracting VVA/GSM impact on patient sexual life as clearly shown by dyspareunia reduction. A further point which should not be overlooked, is the symptoms worsening reported at T3. At this timepoint, maintenance therapy with LMWHA was completely suspended two months before and this could justify the worsening at T3. Indirectly, this event is an evidence that confirms the importance of the maintenance therapy and this plausible considering the chronic nature of menopause. What is most striking about this study, however, is the great effectiveness of this protocol to induce vaginal symptoms improvements. Thanks to this protocol, almost all these patients have reported absence or mild symptoms during the 10 months of treatment and, also, during the follow-up of two months confirming its efficacy on long time.

CONCLUSIONS

In this study, the administration of LMWHA have confirmed results obtained in other works showing not only a great efficacy to improve all symptoms evaluated, but also the ability to maintain these results during the follow-up. The innovative choice behind this study is, undoubtedly, the combined administration of LMWHA both as oral tablets and vaginal suppositories in association with RF/PO sessions. This protocol, indeed, has allowed to improve strongly QoL of VVA/GSM patients. During the first five weeks, the concomitant use of LMWHA administrations and RF/PO sessions has induced a rapid and strong improvement of all symptoms evaluated. Moreover, no exacerbation of symptoms was reported after this period for long time, thanks to the application of a maintenance therapy based only on the administration of LMWHA, confirming its importance for vaginal rehydration and for the avoidance of VVA/GSM symptoms onset. A confirm of this last consideration is the slightly worsening evidenced in the last period of follow-up free of treatments. Thanks to its chemo-physical properties, this protocol resulted useful to improve symptoms perception in a great and stable way. Nowadays, the therapeutic gold standard for VVA/GSM patients is represented by administration of hormonal therapies. However, their application is not always allowed e.g. in presence of oestrogen responsive cancer or when oestrogen levels are normal. For all these reasons, this protocol represents an interesting opportunity for these patients though, considering the limited number of these involved in this study and the absence of a control group, further confirmations are needed to support completely this treatment.

Conflicts of interest:
The authors report no conflict of interest

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