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Microablative CO_2 laser therapy and oral adjuvants in genito-urinary syndrome, effectiveness outcomes: a pilot study

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ABSTRACT

Objective. Genitourinary syndrome is a complex of multi-organ symptoms related to hypoestrogenism. Over 50% of women in menopause are affected by severe symptoms thus the need for new therapeutic approaches. The objective of the study is to demonstrate whether oral integration of bioactive substances in CO_2 laser therapy can enhance the therapeutic effects of genitourinary syndrome.

Materials and Methods. The study conducted is a pilot study of a prospective monocentric case-control type. Sixty patients were recruited and a simple single-blind randomization was conducted to form two homogeneous groups. Half of the patients (group A) underwent CO_2 laser therapy vaginally and received placebo, while the second half (group B) underwent laser therapy and received oral supplementation with hyaluronic acid. Three treatments were administered monthly to each study group. The primary endpoint was the improvement in PISQ-12 scores from the baseline to the six-month follow-up. Secondary endpoints at six months were assessed with a symptom severity scale, PFSQ-7, I-QOL and Vaginal Health Index.

Results. Both groups showed an improvement according to the scores PISQ 12, PISQ 7, Vaginal Health Index (VHI) and Symptom score regarding itching, burning and dyspareunia. Group B achieved greater improvements with statistically significant differences ($p < 0.05$).

Conclusions. The CO_2 laser therapy represents a valid non-hormonal alternative in the treatment of genitourinary syndrome. Oral adjuvant therapies with hyaluronic acid can enhance the effectiveness of vaginal laser therapy.

INTRODUCTION

Genitourinary syndrome of menopause (GSM) is a complex of multi-organ symptoms related to hypoestrogenism that affects women with the onset of menopause. The term was coined at the Consensus Conference in Chicago in 2013 to indicate, in a broader way, the symptoms linked to hormonal depletion and not only genital atrophy [1]. Due to its aetiology, linked to the normal path of female aging, it can be defined as a paraphysiological condition. The extension of life expectancy, the desire for a

better quality of life, greater scientific knowledge and prolonged sexual activity even at an advanced age, push women to experience the symptoms of hormonal depletion for longer and with greater discomfort. Genito-urinary syndrome includes disorders of the sexual sphere such as dyspareunia and of the urinary system such as urgency, dysuria and recurrent cystitis. The female genital tract and the lower urinary tract derive embryologically from the same structure, *i.e.*, the urogenital sinus [2]. The external genitalia and lower urinary tract have common features including widespread exposure of oestrogen receptors. GSM is not just a set of symptoms but rather the reflection of precise tissue remodulations that lead to an impoverishment of collagen fibres in quantity and quality, reduction of elastic fibres and histo-architectural disruption [3].
The discomforts experienced by menopausal women in the urogenital area affect over 50% of the female population, despite the fact that the problem is still underdiagnosed and undertreated [4]. A recent survey conducted in Italy revealed, unsurprisingly, that only a small number of physicians possess the necessary competencies in the matter [5].
It is important to acknowledge the concurrent rise in both the incidence of breast cancer and the number of women who survive it. Consequently, in the forthcoming decades, a significant portion of patients will likely experience vulvo-vaginal and lower urinary tract disorders [6]. This last category of women is the most difficult to treat due to the absence of established safety profiles in the vaginal application of topical estrogens among survivors. Local hormones are the most effective therapy to date. Topical hyaluronic acid, lubricants and moisturizing creams, polynucleotides and platelet-rich plasma can be valid alternatives in the therapeutic plan.
In recent years, vulvovaginal laser therapy has received excellent feedback regarding its outcomes, improving the quality of life and sexual satisfaction of women who accepted this treatment [7]. A 2022 review analysed 312 studies on laser therapy and found only 9 to have a strong scientific basis. The results of these studies agree that fractional CO_2 laser is an effective therapy, enhancing clinical symptoms of GSM and sexual life. An improvement of VAS scale score was reported in all studies [8]. The outlook for treating stress urinary incontinence is also promising [9], although the extant literature presents greater uncertainty in this regard, leaving ample room for classic methods such as urethral slings or bulking agents [10].
According to Di Donato *et al*., women's satisfaction with laser treatment is high: 89.7% of patients would highly (value 5-7) recommend the procedure and 94.9% would be ready to repeat the procedure to maintain results [11]. Therefore, vaginal laser treatment can be considered both an effective and safe innovative therapy for the minimally invasive treatment of symptoms of GSM [10, 12]. During the treatment period, no severe complications occurred. A minority of patients reported mild complications (dysuria, dizziness, minor bleeding, mild discomfort during and after the therapy), but these resolved without the need for treatment [13]. The strong point of this therapeutic option is its safety even in women who have survived hormone-responsive tumours.
Our study stems from the desire to improve the effectiveness of laser therapy by combining various pharmacological and non-pharmacological solutions that are currently scientifically validated. The beneficial effect of hyaluronic acid on genital mucous membranes, for example, has been proven by the results obtained with its local application in gel form [14]. It is also beneficial when taken orally in the treatment of skin aging, mucous membranes and joint connective tissue [15]. The efficacy of vitamins in regulating connective tissue has likewise been demonstrated [16]. The quality and quantity of collagen fibres, in fact, are influenced by the levels of vitamin C [17], and further by those of N-Acetyl-D-Glucosamine [18, 19]. Moreover, the combination of hyaluronic acid and chondroitin sulphate reduces the inflammatory and degenerative status of the tissues [20].
It is therefore reasonable to think about enhancing the effects of vaginal laser therapy through all these adjuvants, which have been substantiated by scientific literature. Undoubtedly, hyaluronic acid (HA) is the protagonist among all bioactive molecules, due to the multiple functions it performs in the repair of tissue lesions. Regarding the possible integration of hyaluronic acid, it is widely demonstrated that the forms with low molecular weight (between 150-300 kDa) act on the differentiation mechanism of fibrocytes and on the expression of metallo-elastases by macrophages, degrading possible bacteria and promoting a protective effect. No study in the scientific literature has addressed the therapeutic possibility of combining vaginal laser treatment with oral supplementation of non-hormonal bioactive molecules. To date, hyaluronic acid is mainly used locally with newly developed equipment such as Vagy Combi and Caress Flow [21].

In the future, laser therapy will represent an increasingly valid and widespread therapeutic opportunity, especially if scientific knowledge leads to more standardised and targeted recruitment protocols. Currently, this type of therapy is regarded as third-line in cancer survivors, after non-hormonal and local hormonal therapies. The increasing scientific consensus regarding the safety and efficacy of CO_2 laser therapy [22] will certainly lead this approach to become the second viable therapeutic option, even prior to the utilisation of topical hormones. Tailored Treatment-Based Approach are the future of GSM [23].

MATERIALS AND METHODS

The study is of prospective monocentric type and has been approved by the International Review Board of the University of L'Aquila with protocol number 17/2023. The study was conducted at the San Salvatore Hospital in L'Aquila, in the urogynaecology clinic. It involved 60 menopausal patients, aged between 50 and 70 years (mean age 59.1 ± 6.2 years), suffering from mild stress urinary incontinence and vaginal atrophy. The mean BMI was 23.6 ± 3.3.
Eligible patients were randomly assigned to two study groups using a randomised procedure based on the decision of the physician in charge. The clear definition of inclusion and exclusion criteria, along with the random selection process, ensured the homogeneity of the sample cohort and the methodological validity of the comparison between groups. The study population have thus a simple single-blind randomization. All patients signed an informed consent form to participate in the research group.
The study population included women aged between 50 and 70 with vaginal atrophy following physiological or iatrogenic menopause and mild stress urinary incontinence that did not require surgical correction. All patients tested negative in pap tests performed in the last two years, vaginal and cervical swabs in the last month, and urine cultures in the last month. Furthermore, patients had to have suspended any local or systemic therapy related to the pathology for 3 or more months. Women with the following conditions were excluded from recruitment: heritable disorders of connective tissue, undiagnosed abnormal uterine bleeding, ongoing tumour pathologies, lack of sexual activity, previous pelvic radiotherapy or previous radiofrequency therapy (**Table 1**).

Table 1. *Inclusion and exclusion criteria.*

Inclusion criteria	Exclusion criteria
Vaginal atrophy following physiological and/or iatrogenic menopause and mild stress urinary incontinence that does not require surgical correction.	Genetic pathologies of the connective tissue.
Age between 50 and 70 years.	Undiagnosed AUB.
Negative PAP TEST performed in the last two years.	Current tumor pathologies.
Suspension of any local or systemic therapy relating to the pathology for 3 or more months.	Lack of sexual activity.
Negative vaginal and cervical swabs in the last month.	Previous pelvic radiotherapy.
Negative urine culture in the last month.	Previous radiofrequency therapy.

This study aims to find new ways to push laser therapy to greater efficacy profiles than those recorded to date without altering its safety profile; exploiting the beneficial properties of some bioactive molecules, in particular, low molecular weight hyaluronic acid. In the population studied, no distinction was made between women with physiological menopause and those with iatrogenic menopause.
One group then underwent the pure microablative CO_2 vaginal laser treatment, *i.e.* without local or systemic adjuvants (group A). In contrast, the second group (group B) underwent the same laser therapy and also took an oral supplement. In group A, which only underwent endovaginal laser therapy, a placebo was administered to avoid possible psychological biases. All the patients in group B declared that they had taken the Jalorest tablets continuously.
The laser therapy consisted of complete vaginal irradiation at an energy level of 90, 85 and 80 mJ/pixel, administered every 30 days for three consecutive months. During the three-month period of laser therapy, women in group B also took one tablet per day of a supplement containing 100 mg of hyaluronic acid from sodium hyaluronate, 400 mg of chondroitin sulphate, 200 mg of N-Acetyl-D-Glucosamine and 80 mg of Vitamin C. The commercial name of the supplement was Jalorest and it was identified for the right mix of components in terms of type and quantity, as compared to the extant scientific knowledge on the synthesis of collagen and the extracellular matrix. In particular, it was appreciated for the low molecular weight hyaluronic acid it contains. The pill of group A, however, did not contain pharmacological principles but only starch.

The primary endpoint was the improvement in PISQ-12 scores from the baseline to the six-month follow-up. Secondary endpoints at six months were assessed with a symptom severity scale, PFSQ-7, I-QOL and Vaginal Health Index.

Before starting any therapy (time zero, *i.e.* t_0), all patients were invited to privately complete internationally validated tests to investigate general, urinary, sexual and vaginal well-being. The following questionnaires were filled:

- I-QOL (Incontinence Quality of Life) for urinary problems.
- PISQ-12 (The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire) for sexual problems.
- PFIQ7 (Pelvic Floor Impact Questionnaire Short form 7) for problems related to alterations of the pelvic floor.
- Vas Symptom Score scale to describe the severity of the perceived vulvo-vaginal symptoms. The VAS Symptom Score scale was designed to evaluate symptoms such as vaginal irritation/itching, sensation of dryness, local discomfort, pain of the part and dyspareunia, with a score ranging from 1 to 10.

These tests were administered once more at the follow-up conducted six months later, *i.e.* three months after the end of the final laser session (time t_1).

The last parameter taken into consideration at time 0 and time 1 was the Vaginal Health Index, which, through the analysis of five parameters (vaginal elasticity, vaginal secretions, pH, epithelial mucosa, vaginal humidity), immediately allowed to diagnose and prove the severity of vaginal atrophy. This diagnostic index ranges from a minimum score of 5 to a maximum of 25, with each parameter evaluated on a scale from 1 (none) to 5 (excellent). A total score of less than 15 is indicative of vaginal atrophy.

Statistical evaluations were conducted using both parametric and non-parametric tests for paired data. The t-student test and the Wilcoxon rank-sign test were used respectively after evaluating the normality of the distribution of the variables with the Shapiro-Wilk test. A sample of 60 patients is sufficient to identify a statistically significant difference (between pre- and post-treatment) in the endpoints for a percentage of at least 40%, with a statistical power of 0.80 and a significance level α of 0.05. The calculation of the sample size was performed with the G*Power3.1.9.7 program.

RESULTS

At the beginning of the study (t_0), all patients underwent the tests and evaluations described previously. At six months (t_1) the results were compared between the two groups examined: group A, treated with laser therapy/placebo, and group B, treated with the combination of laser therapy and the food supplement. In order to facilitate comprehension, group A will henceforth be referred to as the "laser therapy alone group". The administration of placebo pills to this group is to be implied.

An improvement was observed in the local and general status of patients in both groups. In particular, patients who consumed the supplement presented more satisfactory results. As illustrated in **Figure 1**, the group that received oral integrative therapy experienced a superior improvement in their quality of sexual life. The PISQ-12, in fact, attests to this result in **Figure 2**, where the increase in its score is significant in group B. As further evidence of this phenomenon, a greater reduction in PFIQ 7 emerged in group B compared to group A. Group B also had a significant decrease in the score of the SYMPTOM SCORE scale, in the areas of

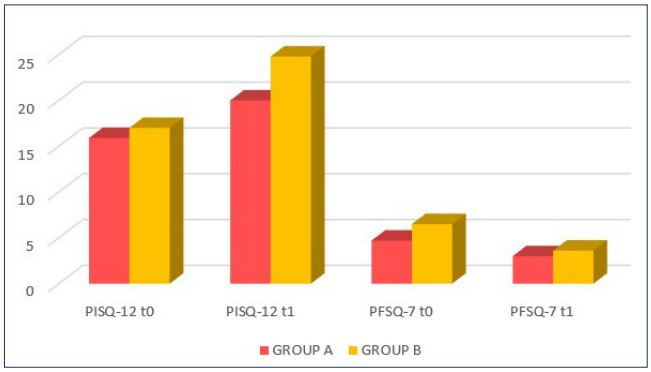

Figure 1. *The graph shows how the PISQ-12 score improves more in group B, while the PFSQ-7 score decreases more. Patients who use oral supplementation improve the most.*

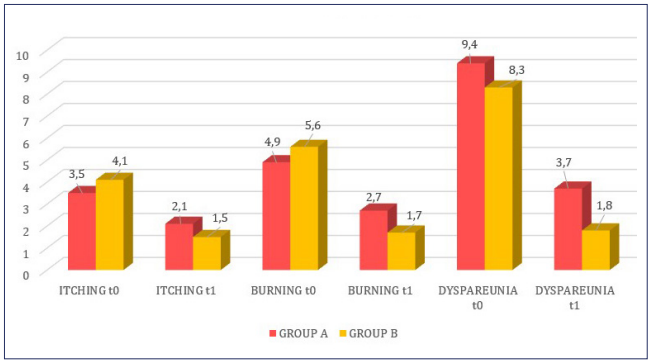

Figure 2. *All symptoms related to vaginal atrophy found improvement, especially in group B patients.*

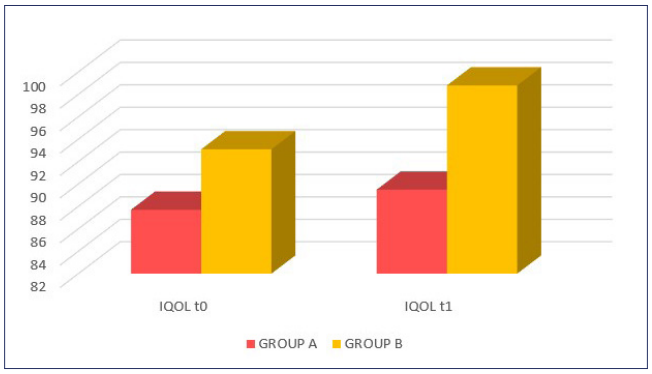

Figure 3. *Patients who took hyaluronic acid experienced a greater decrease in episodes of urinary incontinence.*

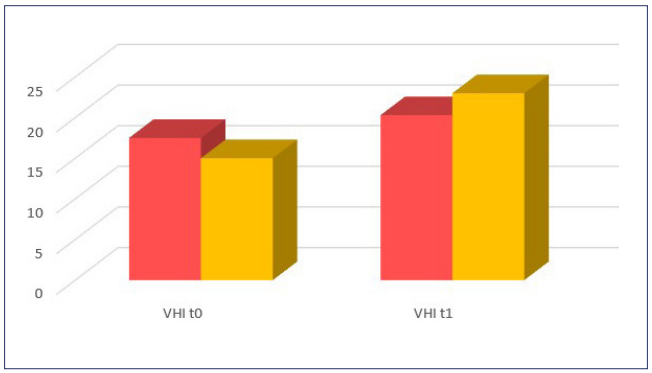

Figure 4. *Statistically significant increase in the VHI score with oral supplementation of hyaluronic acid.*

itching, burning and dyspareunia ($p < 0.05$). The difference in efficacy was also statistically significant compared to group A. As regards the pain symptom, both groups exhibited an improvement in their conditions, but the difference between the two groups was not statistically significant. It can thus be stated that microablative CO_2 laser therapy does not reduce pain more effectively when associated with hyaluronic acid. This datum is understandable considering that the integrated molecules do not have neurotrophism. The addition of supplements such as Palmitoylethanolamide (PEA) and Acetyl-L-carnitine would probably have led to a greater therapeutic surplus.

The most recent data describe an appreciable improvement in the patient's quality of life, based on their urinary and genital problems, as regards normal daily life activities and their state of mind.

As can be seen in **Figure 3**, the double treatment was associated with a significant improvement ($p < 0.05$) in I-QOL scores in the analysed menopausal women suffering from mild to moderate SUI, compared to laser treatment alone. In group A, the IQOL score increased by 2.01%, while in group B it increased by 5.77%. Although both groups experienced an improvement in symptoms, especially when hyaluronic acid was added, laser therapy generally had little impact on urinary symptoms, unlike what is reported in the scientific literature [24].

An objective and statistically significant increase in the VHI score was found with more encouraging results in group B: the average score increased from 12 pre-treatment to an average of 20 six months later ($p < 0.05$). This evidence is shown in **Figure 4**.

The laser treatment combined with the oral administration of hyaluronic acid and other bioactive compounds was well tolerated by all patients. No *de novo* side effects were found in group B compared to those typically associated with laser therapy. The most significant side effect was the perception of pain after laser therapy. None of the patients interrupted treatment due to excessive discomfort and there was no significant statistical difference between the two groups.

DISCUSSION

The study evaluates through numerical scores the difference in effectiveness in terms of quality of life, sexuality and symptoms in women suffering from genitourinary syndrome. Both groups showed an improvement after the treatment, but a better result in terms of symptom reduction and improvement in the state of vaginal mucosa was demonstrated in patients who received laser therapy combined with the food supplement. Dyspareunia presented the best resolution, which had a strong impact on women's general and marital well-being. Patients reported a reduction in pain related to sexual intercourse, a reduction in bleeding due to mechanical rubbing on the atrophic mucosa and an increase in lubrication during sexual intercourse and in everyday life. Not coincidentally, the PISQ-12 also showed improvements. Patients who reported recurrent cystitis at the start of treatment experienced an improvement in their condition after six months, with a reduction in frequency and dysuria. This was also followed by a reduction in the use of antibiotics to treat recurrent or presumed cystitis by women.

Patients with mild-moderate stress incontinence at the start of treatment, assessed with the I-QOL questionnaire, benefited from an improvement in symptoms, with a reduction in urinary losses and an enhanced quality of life. The patients' quality of life post-treatment was evaluated using the PFIQ-7

questionnaire. These scores were assessed during a medical examination in accordance with the stated results. During the gynaecological examination, it was possible to evaluate the mucosa's increased elasticity, resistance and lubrication. In patients who experienced severe pain and bleeding prior to treatment when the speculum was inserted, clinical improvement was observed after treatment. Over the months of the therapy, the vaginal pH decreased, and in some cases, it returned to the range of 3.5 to 4.5.

The results are satisfactory and demonstrate the increased effectiveness of laser therapy when used alongside adjuvants, such as oral supplements. No major adverse events have been reported in either group.

A weakness of the study is its limited sample size of 60 women, although this still allows for a good statistical analysis. While the total sample size was adequate for an initial clinical exploration, its relatively small size may have limited the statistical power of the analysis, preventing the detection of significance for differences, relevant on a clinical level nonetheless. The randomisation adopted procedure (random clinical choice by the physician) allowed for balanced assignment, but was not performed using blinded computerised randomisation to ensure blind assignment. This meant that there was a potential, albeit low, risk of selection bias. However, the homogeneity of the two groups with regard to basic characteristics (age, associated diseases, BMI, *etc*.) suggests that this risk was limited.

Scientific research has shown that hyaluronic acid with a lower molecular weight (LMW-HA) is more easily absorbed by tight junctions. It has been demonstrated that only LMW-HA with a molecular with a molecular weight of 5 kDa or lower can easily cross the intestinal barrier and reach the systemic blood circulation [25]. The hyaluronic acid used in our supplement, ExceptionHYAL (Hyaluronic acid from Sodium hyaluronate), has a molecular weight of 200-600 kDa, making it optimal for absorption. The creation of molecules with a lower molecular weight certainly represents a fertile area of research for achieving better results thanks to oral supplementation. Our study, the first to evaluate the usefulness and safety of supplementation with bioactive molecules, represents an interesting starting point. The combined effects of laser therapy and hyaluronic acid have never been studied before; on the contrary, the two therapies have been compared, demonstrating the individual effectiveness of both [26]. Only the effectiveness of combining hyaluronic acid with radiofrequency therapy has already been proven [27].

The data expressed in the study are numerical, based on scores, making the study objective and reproducible. The tests used are validated at an international level, though they can be influenced by the emotional and psychological sphere of the patient. The possible bias of the placebo effect was avoided by administering tablets without hyaluronic acid to the control group as well. Similarly, the Vaginal Health Index is an operator-dependent score. It would be interesting, therefore, to analyse the histological differences of the mucous membranes of patients in groups A and B. Ethical limits, however, make this path difficult to follow.

Menopause is a chronic condition for which the positive effects produced will naturally tend to regress. A longer period of study will allow us to understand the times of regression and the methods and frequency of reintervention. In the future, it may be possible to observe whether oral administration of hyaluronic acid alone is capable of maintaining the results obtained after treatment over the long term. It has been proven that prolonged administration of hyaluronic acid does not cause health problems [28]. Microablative CO_2 laser therapy is also considered safe and effective, although numerous research protocols are being developed to provide definitive data.

CONCLUSIONS

This study demonstrates that combining adjuvants with endovaginal laser light during treatment provides a significant advantage. Although statistical significance was not achieved in all parameters studied due to the limited sample size, the emerging patterns are consistent with recent studies and with the physiological picture of the role of hyaluronic acid (HA) in counteracting genitourinary syndrome. This shows pathophysiological and clinical consistency in favour of HA supplementation, with potential benefits in terms of response times and treatment efficacy.

These scientific data are precious for the niche of patients less responsive to laser therapy, thus being able to find a greater boost in the resolution of their urogenital problems. The use of low molecular weight hyaluronic acid orally finds, therefore, a scientific rationale confirmed in the data shown in our

research, providing an important starting point for further prospective studies on larger samples.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution
A.D.A.: Conceptualization, supervision, project administration. A.S.: Investigation, writing – original draft, writing – review & editing, resources, visualization. M.G.: Methodology, supervision. A.T.: Data curation, formal analysis, investigation, resources.

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Study registration
N/A.

Disclosure of interests
The authors declare that they have no conflict of interests.

Ethical approval
The study is conducted with approval of research protocol N 29932 of the Ethics Committee of the University of L'Aquila. The study is in line with the main ethics standard.

Informed consent
Patient consent was obtained in written format with autobiographical signature.

Data sharing
All scientific data are stored anonymously at the Pelvic Centre of the San Salvatore Hospital in L'Aquila. The data are available under reasonable request to the corresponding author.

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