

Short-term effect of vaginal erbium laser on the genitourinary syndrome of menopause

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Aim. In this study we evaluated the short term effects of vaginal erbium laser (VEL) in the treatment of postmenopausal women (PMW) suffering from genitourinary syndrome of menopause (GSM).

Methods. Sixty-five PMW were evaluated before and after VEL treatment (1 treatment every 30 days, for 3 months). GSM symptoms were evaluated either with subjective (Visual Analog Scale, VAS) and objective (Vaginal Health Index Score, VHIS) measures. In addition, in 21 of these PMW suffering from mild-moderate stress urinary incontinence (SUI), the degree of incontinence was evaluated with the International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF) before and after VEL treatments.

Results. VEL treatment induced a significant decrease of VAS of both vaginal dryness, dyspareunia ($P<0.01$) and a significant ($P<0.01$) increase of VHIS). In addition, VEL treatment induced a significant ($P<0.01$) improvement of ICIQ-SF scores in PMW suffering from SUI. VEL was well tolerated with less than 2 % of patients discontinuing treatment due to adverse events.

Conclusion. VEL treatment significantly improves vaginal dryness, dyspareunia and mild-moderate SUI. Larger and long-term studies are needed to investigate the role of laser treatments in the management of GSM.

KEY WORDS: Menopause - Atrophy - Urinary incontinence, stress.

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The genitourinary syndrome of menopause (GSM) is the new definition for the variety of menopausal symptoms associated with physical changes of the vulva, vagina, and lower urinary tract, related with estrogen deficiency.¹ The symptoms related to GSM include vaginal dryness, burning, irritation, lack of lubrication, dyspareunia, as well as urinary symptoms of urgency, dysuria and recurrent urinary tract infections.¹ The signs and symptoms of GSM affect up to 50% of postmenopausal women (PMW); they are chronic and are expected to worsen over time, interfering with sexual function and quality of life.²⁻⁶ Hormone replacement therapy (HRT) induces effective, rapid and long-term relief, with the local vaginal estrogen administration the treatment of choice for the sole treatment of vaginal atrophy.^{7, 10} Although systemic risks have not been identified with local low-potency/low-dose estrogens, long-term efficacy and safety data are lacking. In addition, many women do not accept extended HRT, or may have contraindications, as a personal history of breast cancer.⁷⁻¹⁰ New management strategies for GSM are needed in order to enable women to choose among

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different options, considering the benefits and risks associated with each strategy.

Salvatore *et al.*¹¹ reported that a treatment with the microablative carbon dioxide (CO₂) laser may improve vaginal health in PMW. This seminal paper actually discloses a new era for non-hormonal treatment of GSM. Indeed, we have to consider that various lasers possess diverse properties, that can be usefully applied in different conditions. The non-ablative Erbium laser technology may provide a non-invasive treatment option, and it is widely used for surgical treatments in dermatology, dentistry and aesthetic medicine.¹¹⁻¹⁶ The aim of the present study was to evaluate the short-term effectiveness and acceptability of vaginal erbium laser (VEL) as a new, second generation, non-ablative photothermal therapy for the treatment of GSM.

Materials and methods

This study was performed in 67 PMW suffering from GSM, attending the outpatient Menopause Clinic of Pisa University Hospital. The protocol was approved by the Division Ethics Committee and reviewed by an Independent National Advisory Board. Inclusion criteria were: the presence of a GSM in healthy postmenopausal women (at least 12 month since last menstrual period or bilateral ovariectomy) with plasma gonadotropin and estradiol levels in the postmenopausal range (FSH >40 U/L; estradiol <25 pg/mL) and negative PAP smear. Exclusion criteria were vaginal lesions, scars, active or recent (30 days) infections of the genitourinary tract; abnormal uterine bleeding; use of vaginal preparations within the 30 days prior to the study; history of photosensitivity disorder or use of photosensitizing drugs; genital prolapse (grade III-IV according to the Pelvic Organ Prolapse Quantification, POP-Q, system classification); serious or chronic condition that could interfere with study compliance; treatment with hormones to relieve menopausal symptoms in the 12 months before the study.

At the first visit the eligibility of the patient was verified, the written informed consent

was obtained, and the sociodemographic and clinical characteristics were collected. Subjective symptoms (vaginal dryness and dyspareunia) were evaluated by a Visual Analog Scale (VAS) at every visit (range 0-10 cm, 0=total absence of the symptom and 10 cm = the worse possible symptom). In addition, at each visit during the gynecologic examination the Vaginal Health Score Index (VHIS). VHIS evaluates the appearance of vaginal mucosa (elasticity, pH, vaginal discharge, mucosal integrity and moisture). Each parameter is graded from 1 to 5 being atrophic a total score ≤ 15 .²⁸

All patients gave a written informed consent. All subjects were treated with VEL, a non-ablative solid state Erbium in yttrium aluminum-garnet crystal (Er:YAG) Laser (Fotona Smooth™ XS, Fotona, Ljubljana, Slovenia) with a wavelength of 2940 nm. The parameters were selected based on extensive preclinical and clinical studies controlling the energy and pulse duration simultaneously.²⁵ This technology (SMOOTH™ mode) with a sequence of low fluence and longer-shaped Erbium pulses, distributes the heat approximately 100 microns deep into mucosa surface, achieving a controlled deep thermal effect, without ablation. Therefore, the SMOOTH™ mode pulses allow controlled tissue heating, in a safe and harmless ambulatory procedure without ablation and carbonization of the tissues, practically avoiding the risk of perforation with accidental lesions of urethra, bladder or rectum. The laser parameters (RenovaLase®, Phase 1) are settled to deliver 8.5 J of laser energy with the Smooth mode pulsing sequence using 7 mm spot. Briefly, after inserting a specifically designed vaginal speculum, the probe is inserted into the speculum, with no direct contact with the vaginal mucosa. Thus circular irradiation of vaginal wall is performed with laser energy delivered every 5 mm (using the graduated scale on the probe), retracting the probe till the vestibule. This procedure is repeated 3 times rotating the speculum by 45° each time. Finally, after removing the speculum and using a different probe, the vestibule and introit are irradiated with a fractional 7 mm Smooth mode laser

beam, delivering 3J of laser energy. Such laser beam is manually scanned around vestibule and introitus with slight overlapping of individual spots until three passes are executed (RenovaLase®, Phase 2). After treatment, patients are recommended to avoid sex intercourse for one week. Twenty one of these patients were suffering also from stress urinary incontinence (SUI) and the degree of incontinence was assessed with the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF), where a maximum score of 21 represents permanent incontinence. None of these patients presented a pelvic organ prolapse greater than stage II, according to the Pelvic Organ Prolapse Quantification (POP-Q) system classification. These patients during the VEL procedures were submitted also to additional laser treatment of anterior vaginal wall (IncontiLase® Phase 1 procedure), specifically designed for urinary incontinence, with a fractionated Smooth mode beam, delivering 3J of laser energy.

The VEL procedures were performed in an outpatient clinical setting. No specific preparation, anesthesia, or post treatment medications were prescribed. Before the procedures the vagina was cleaned with a swab. Patients were treated with 3 laser applications, (L1, L2, L3) every 30 days, with screening visit 2 to 4 weeks prior the first laser treatment (baseline) and follow up visits after 4 weeks from the last laser application (T+4). The women were asked to evaluate the acceptability of the therapy. Women were asked to assess the general acceptability, efficacy of the finalized therapy as excellent, good, acceptable, bad, or unacceptable. Being an exploratory study, the sample size was not based on a statistical rationale. The sample size was planned to be similar to those of published data.¹¹ All the results are reported as the mean±SE of absolute values.

Statistical analysis

Baseline values were compared by Student's t-test. Two way analysis of variance for repeated measures and factorial analysis of variance were used to test the differenc-

TABLE I.—Baseline characteristics of 65 participants who completed the study. Data are expressed as a mean±SD.

Age (years)	62.9±8.1
Age at menopause	53.3±5.1
Years since menopause	15.5±4.4
Body mass index (kg/m ²)	27.5±2.3
FSH (IU/L)	74.4±10.8
Estradiol (pg/mL)	25.4±4.3

es within and between the groups, respectively. The *post hoc* comparison was made by Scheffe F-test, using the Sigma Stat View software (SPSS Science, Chicago, IL, USA).

Results

The age, age at menopause and years since menopause, Body Mass Index (BMI) and basal hormone levels are reported in Table I. A total of 65 patients completed the study; one patient left the study for personal reasons; one complaining the discomfort related to the first application. The VAS scores for vaginal dryness and dyspareunia showed a significant ($P<0.01$) decrease 4

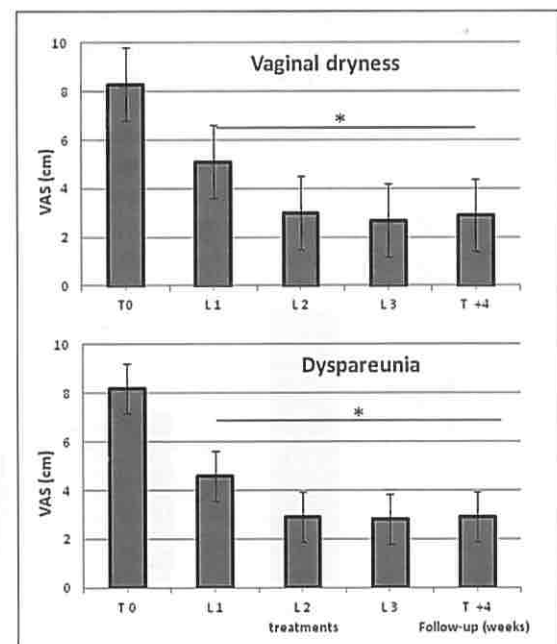


Figure 1.—Effect of second-generation laser thermotherapy on vaginal dryness (A) and dyspareunia (B) (N.=65). * $P<0.01$ vs. corresponding basal values; see text for details.

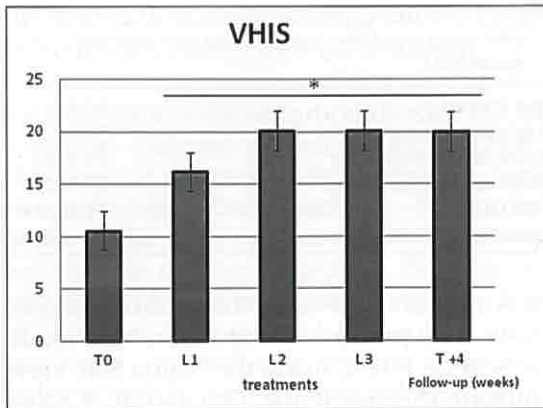


Figure 2.—Effect of second generation laser thermotherapy on VHIS (N.=65).

* $P < 0.01$ vs. corresponding basal values in both groups; see text for details.

weeks after VEL treatment (Figure 1). The difference from baseline values for dryness and dyspareunia was statistically significant ($P < 0.01$) during the follow-up period (Figure 1). In addition also the VHIS significantly ($P < 0.01$) increased (Figure 2). The values measured 4 weeks from the last VEL application were significantly ($p < 0.05$) different from corresponding basal values (Figure 2).

In the 21 patients suffering from SUI the VEL treatment induced a significant ($P < 0.01$) decrease in the ICIQ-SF scores (Figure 3).

The ICIQ-SF scores remained significantly ($p < 0.01$) lower than basal values at T+4 (Figure 3).

In the 65 valid completers in the VEL group, 55 patients (84.6 %) defined the procedure excellent-good, 7 patients (10.7%) acceptable, 3 patients (4.6 %) reported their experience as bad, only for the first application.

Discussion

The results of this prospective study indicate that VEL treatment can ameliorate the signs and symptoms of GSM. The reduction in the subjective scores and the objective improvements were rapid and evident after the first laser application. VEL treatment was well tolerated by women who subjectively perceived a rapid clinical benefit that was confirmed by the objective improvement of the vaginal milieu, as measured by the VHIS. Salvatore *et al.*¹¹ demonstrated that the microablative CO₂ laser energy is effective to improve vaginal dryness as well as dyspareunia, in a 12 weeks follow-up study. Our data clearly indicates that also the Erbium laser is effective in the therapy of GSM, as previously reported in abstract form.²⁶ As with the CO₂ procedure, our

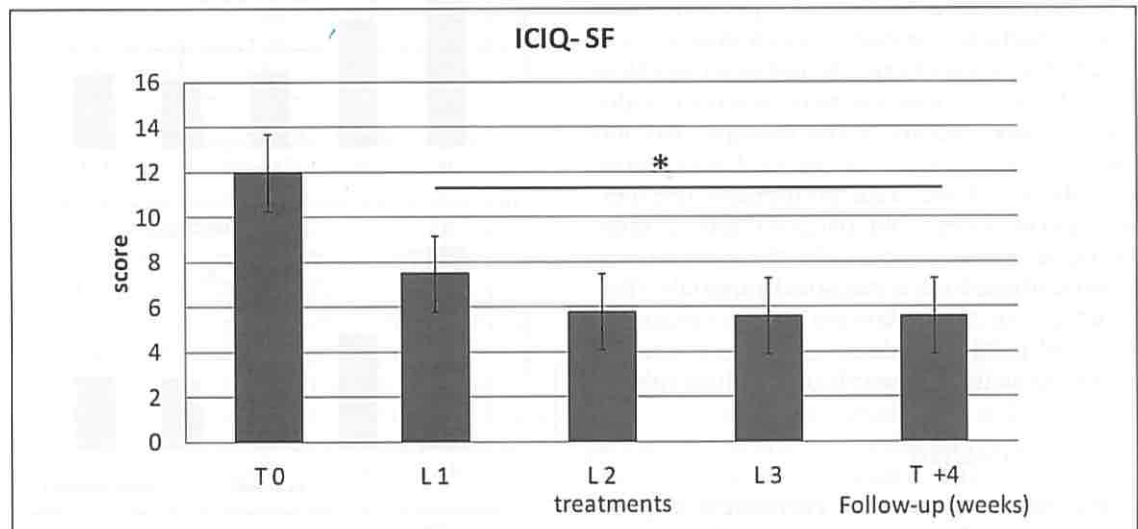


Figure 3.—Effect of second generation laser thermotherapy on International Consultation on Incontinence Questionnaire (ICIQ-SF) score in 21 PMW suffering from stress urinary incontinence.

* $P < 0.01$ vs. corresponding basal values; see text for details.

two-step protocol the laser irradiation was applied first into the vaginal canal and after at the introitus area. At variance, the VEL procedure is performed using special vaginal speculum introduced as a guide for the handpiece laser beam delivery system. Thus, the patients do not feel the several longitudinal passes performed using a step-by-step retraction of the handpiece. No anesthesia was necessary and only 3 patients reported the first laser application experience as bad. Conversely, after the first treatment, VEL effects on vaginal mucosa induced an ideal treatment compliance. The innovative techniques used in the VEL procedures can guarantee not only the efficacy, but also, mainly, an intrinsic safety, since the Erbium beam cannot damage the tissues in depth, eliminating the risk of tissue necrosis, in a non-ablative form, without cut, abrasion or bleeding.^{16, 17} This characteristic makes Erbium laser an ideal candidate for the thermal treatment of the vaginal walls.¹⁶⁻²⁰ In addition, as previously reported by other authors,¹⁷⁻²⁰ our data suggest that VEL treatments can be of help in PMW suffering from mild-moderate SUI. In fact, in PMW suffering from GSM referring also mild to moderate SUI, the VEL improved the ICIQ-SF scores. The VEL technique allows several passes on the vaginal canal that are necessary for the treatment of the anterior vaginal wall in women suffering from SUI. The VEL technique, with a controlled rise in tissue temperature, induces vasodilation and collagen remodeling and neocollagenesis.¹²⁻¹⁶ Since the VEL technique is comfortable for the patient, the use of high fluences with highly collimated fractionated beams is well tolerated. With the VEL the vaginal anterior wall is treated with several passes that could not be possible without anesthesia, in an outpatient setting if the patients were suffering from the procedure. The effect of VEL on SUI is of particular interest. Urinary incontinence is a common and important health care problem that is underreported, underdiagnosed, and therefore undertreated in women. The treatment of SUI is a major challenge for women's health and quality of life. Nonpharmacologic management

for SUI, such as pelvic floor muscle training is effective, can improve UI and may provide complete continence, but many patients discontinue the treatment. Present data confirm that VEL might be useful for the noninvasive treatment of SUI.¹⁸⁻²⁰ Our study has several limitations, including the sample size, but mainly the absence of a sham, blank treatment. Obviously, future well-designed and controlled studies are needed to validate the use of VEL for SUI.

Conclusions

Taken together, these data clearly suggest that VEL can be offered as a new, second generation, non-ablative photothermal therapy for the treatment of GSM. Further studies will help to better define the role of VEL for the treatment of GSM and SUI.

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Conflict of interest.—During the past 2 years, Dr Gambacciani had financial relationships (lecturer, member of advisory boards and/or consultant) with Bayer Pharma, Merck Sharpe & Dohme, Pfizer Inc, Teva/Theramex. Dr Levancini reported no conflict of interest.

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