Fractional-Pixel CO_2 Laser Treatment in Patients With Urodynamic Stress Urinary Incontinence: 1-Year Follow-Up

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Background and Objectives: Vaginal pixelated low power and long pulses (LPLP) CO_2 laser has been suggested as an optional treatment for stress urinary incontinence (SUI) with many studies reporting short-term improvements. The objective of this study was to assess the 1-year subjective and objective efficacy of vaginal CO_2 laser in women with urodynamic SUI.
Study Design/Materials and Methods: This was a prospective multicenter study. Patients with confirmed urodynamic SUI graded as mild or moderate were included. We used three sessions of fractional pixelated CO_2 laser for vaginal application and followed up the patients at 6 and 12 months. We used the following measures at follow-up: 1-hour pad test (ICS protocol), questionnaires including Pelvic Floor Distress Inventory 20 (PFDI-20), Pelvic Floor Impact Questionnaire (PFIQ), Patient Global Impression of Improvement (PGI-I), and a 3-day urinary diary. The urodynamic assessment was repeated at 6 months.
Results: Fifty-two patients with SUI had three laser treatments, of whom 48 completed a 6-month follow-up and 42 patients completed 12-month follow-up. No serious adverse events were recorded during the study period. A significant reduction on the 1-hour pad test was found from baseline (6.3 ± 1.6 g) to the 12-month follow-up (3.7 ± 1.4 g, $P < 0.05$) was found. PGI-I showed 75.0%, 61.9%, and 64.3% improvements at 3, 6, and 12 months, respectively. PFDI improved significantly and consistently from baseline until 12 months (37.2 ± 3.89 to 16.1 ± 3.7, $P < 0.05$). Similarly, PFIQ showed significant improvements from the first treatment up to 12 months. Urodynamic assessment at 6 months showed that 41.4% of patients had no stress incontinence.
Conclusion: The vaginal CO_2 laser was found to be effective for mild-to-moderate SUI over a follow-up period of 1 year, according to a variety of objective and subjective parameters. The wide range of parameters enables optimal patient consultation and subsequent treatment. Lasers Surg. Med. © 2020 Wiley Periodicals LLC

Key words: urinary stress incontinence; vaginal CO_2 laser; urodynamic assessment; bladder symptoms; quality of life

INTRODUCTION

Stress urinary incontinence (SUI) is a common complaint among women, with an observed prevalence of between 4% and 35% [1]. Although the diagnosis of uncomplicated SUI is based on patient complaints and objective demonstration of stress-related urinary leakage, various objective tests, including urodynamic studies (UDS), have been recommended by international guidelines (ICI = International Consultation for Incontinence; AUA = American Urological Association; SUFU = Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction), particularly in complicated SUI cases before surgical intervention [2,3].

The treatment of SUI ranges from a conservative approach with pelvic floor exercises to surgical treatment, such as mid-urethral tapes or retropubic procedures. Although the outcome of surgical procedures is well-defined [4], most patients are reluctant to undergo surgical intervention to improve their quality of life and are looking for nonsurgical or minimally invasive options. In addition, following the order of the U.S. Food and Drug Administration to all U.S. manufacturers to stop selling and distributing all surgical mesh intended for transvaginal repair, the use of vaginal meshes in urogynecology has been largely scrutinized [5]. The effect on the use of mid-urethral slings (MUS) was dramatic, with obvious downward trends in its use, as reported from England [6].

Vaginal application of CO_2 laser has been recently introduced for medical conditions related to the vaginal epithelium. Most of the studies on vaginal CO_2 laser have been performed for various symptoms under the newly defined broad term "genitourinary syndrome of menopause" (GSM) [7–9] and very few have assessed the

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efficacy in patients with SUI [10–14]. The promising outcome of SUI treatment in these prospective studies was short term, namely 3–4 months [14], 6 months [13], or slightly longer [11,12]. In addition, most of these studies lack well-accepted objective outcome measures. In 2017, Pergialiotis et al. [15] concluded that in 13 studies, there was not enough evidence to recommend laser treatment for SUI, and suggested that future studies should base their findings not only on patient satisfaction but also on urodynamic evaluation to enhance their scientific merit.

The aim of this study was to assess the efficacy of fractional-pixel low power and long pulses (LPLP) CO_2 laser for SUI over a 1-year follow-up period, using a well-accepted objective and subjective outcome measures, including urodynamic assessment.

MATERIALS AND METHODS

Study Design

This was a multicenter, prospective, open-label, cohort study conducted in three medical centers between June 2017 and October 2019. The study protocol was approved by the Institutional Review Board in each institution and registered on www.clinicaltrials.gov as NCT02981654. Every patient approved the study protocol by signing an informed consent form before recruitment. Patients were eligible to participate if they had proven urodynamic stress incontinence, were aged 30–75 years, their main urinary incontinence complaint was related to stress, and their severity of incontinence was graded as mild or moderate by the Sandvik score, which consists of two questions regarding frequency and amount of leakage. It categorizes urinary incontinence into slight, moderate, and severe, and correlates well with 24-hour pad test [16].

Volunteers were excluded if they had undergone previous anti-incontinence surgery, had pelvic organ prolapse more than grade 2, or if their body mass index (BMI) was greater than 38. Similar pretreatment assessment and procedures were carried out for all participants, including a urine culture, pap smear, pregnancy test, urodynamic testing, and a thorough gynecological examination.

Patients were followed closely for 12 months from the first laser application. At each treatment session and at follow-up visits (6 and 12 months since the first treatment session), we used the 1-hour pad test, and questionnaires including the Pelvic Floor Distress Inventory 20 (PFDI-20) and the Pelvic Floor Impact Questionnaire (PFIQ), which are well-validated and established questionnaires for pelvic floor disorders symptoms and their impact on the quality of life [17]. The general impression of improvement was assessed each time using the seven-scale questionnaire, Patient Global Impression of Improvement (PGI-I), and scores of 1, 2, and 3 corresponded to "very much better," "much better," and "better" compared with baseline. This questionnaire has a significant correlation with incontinence episode frequency, stress pad test, and incontinence quality of life, as previously reported by Yelcin et al [18]. In addition, a 3-day urinary diary was reported at each visit, a gynecological examination performed, and the Vaginal Health Index (VHI) results were recorded.

Urodynamic studies included uroflowmetry, dual-channel cystometry, and pressure-flow studies on a Life-Tech Urolab system (Life Tech Inc., Stafford, TX). The studies were performed in all participants at baseline according to ICS protocols [19]—the bladder was filled with 6-Fr fluid-filled catheters, and stress-related leakage was measured at 250 cc. Leak point pressures were recorded during cough and Valsalva. At 6 months, patients were asked to repeat the same urodynamic assessment, and only 29 patients agreed to repeat the assessment.

The VHI is a system used to evaluate vaginal health by measuring vaginal elasticity, fluid volume, pH, epithelial integrity, and moisture on a scale of 1 to 5. This is a quantitative measurement tool to assess changes, with scores ranging from 5 (severe) to 25 (normal) across all five parameters.

Vaginal biopsies were taken in 12 patients, at pretreatment, and at the 6-month follow-up. The vaginal biopsies were performed under local anesthesia from the posterior vaginal wall, 2 cm from the vaginal opening. Specimens were analyzed by hematoxylin and eosin staining.

Study Intervention

Participants underwent three intravaginal treatments at least 4 weeks apart with the fractional microablative CO_2 laser system (FemiLift™; Alma Lasers, Caeasria, Israel), based on pixelated low power (0.37 W) and long pulses (100–270 milliseconds) photo-ablative technology allowing mild ablation and major thermal deposition. The laser intensity was adjusted to the patient's tolerance, ranging from 40 to 120 mJ/pixel. The laser beam was fractionated into 81 microbeams (pixels) at each activation (per 1 cm^2). The procedure was repeated three times in each session. The laser beam was applied with a vaginal probe, gently inserted up to the top of the vagina, and subsequently withdrawn at 1-cm intervals while rotated to six positions in each station to provide complete circumferential treatment of the vagina. At the investigators' discretion, an eutectic mixture of local anesthetic cream was applied to the introitus for 10 minutes and wiped clean and dried before vulvar laser therapy. Participants were advised to avoid coital sexual activity for at least 3 days after each laser application.

Statistical Analysis

Descriptive statistics. All measured variables and derived parameters were tabulated by descriptive statistics. For categorical variables, summary tables were provided, noting sample size, and absolute and relative frequency. For continuous variables, summary tables were provided, noting sample size, arithmetic mean, standard deviation, median, minimum, and maximum. Changes from baseline were summarized in tables and figures.

Populations for analyses. The safety analysis set included all subjects who were enrolled and underwent at least one study treatment. The efficacy analysis set included all subjects who were enrolled in the study and completed at least one study treatment. Outcome measures at each treatment session and follow-up visits were compared with baseline and the number of subjects at each session is recorded.

All paired *t* test tests were two-tailed and a *P* value of 5% or less was considered statistically significant. The data were analyzed using the SAS® version 9.3 or higher (SAS Institute, Cary, NC).

RESULTS

Sixty-four patients were screened, of whom eight patients were excluded during urodynamic assessment due to a lack of predefined SUI criteria. Fifty-six patients completed the first treatment and 52 patients had three treatments, of whom 48 patients attended the 6 months follow-up and 42 completed the 1-year follow-up.

Patient demographics of the group that completed 1-year follow-up are shown in Table 1. The patients' mean age was 49.1 (range: 32–73) years, parity was 2.5 (0–5), 13.6% were smokers, and the mean BMI was 27.1 (15–37.2). The group consisted of 68% premenopausal women and 32% were menopausal. The range of pad weight at baseline was 0–59 g (mean: 7.7 g), and the incontinence severity score was moderate in 83% at baseline.

No serious adverse events were recorded during the procedure or at the 12-month follow-up. Minor side effects that were related to treatment included: transient vaginal secretion (22 patients, 38.6%), vaginal irritation (one patient), transient fever (one patient), and urinary tract infection (UTI) (one patient). At 1-year follow-up, the procedure was found safe, with no adverse events noted.

The mean laser energy changed slightly from one treatment session to another (at first, second, and third treatment session). The total laser energy was calculated by mJ/pixel multiplied by 81 (the number of microablative spots) multiplied by the number of laser activations per individual treatment. The mean total energy per patient increased gradually from the first treatment ($17{,}863.3 \pm 195.3$ mJ/patient) to the last treatment ($20{,}793.2 \pm 240.9$ mJ/patient).

The objective parameters of incontinence included the 1-hour pad test and the number of incontinence episodes. A significant reduction was recorded for pad weight changes from baseline to the third treatment, the 6-month follow-up, and the 12-month follow-up (Fig. 1). Mean pad weight was reduced significantly from baseline to the 12-month follow-up (6.3 ± 1.6 to 3.7 ± 1.4 g, $P < 0.05$). However, the mean number of incontinence episodes during 3 days of monitoring dropped significantly only after the third treatment (5.8 ± 0.9 to 3.5 ± 0.8, $P < 0.05$), and did not reach significant levels at 6 and 12 months.

Urodynamic studies confirmed the diagnosis of stress incontinence in all patients, and the range of leak point pressures on baseline urodynamic assessment was 58–180 cm H_2O. The urodynamic assessment showed a stable detrusor without voiding problems in all patients. The stress-related leak was demonstrated either during coughs (mean cough leak point pressure [CLPP] = 146.9) or Valsalva (mean Valsalva leak point pressure [VLPP] = 123.2). At the 6-month follow-up, 29 patients had repeat urodynamic tests, of whom 12 (41.4%) did not leak. The mean CLPP and VLPP (117 and 104) at 6 months were not different from baseline values in patients who had leakage.

Subjective assessment was based on the PGI-I, which demonstrates a global impression of improvement, showed 75.0%, 61.9%, and 64.3% improvement from the third treatment and at the 6- and 12-month follow-up, respectively. The bladder symptoms, measured by the PFDI score, improved significantly and consistently from the first treatment to the final assessment at the 12-month follow-up (37.2 ± 3.89 to 16.1 ± 3.7, $P < 0.05$). The most significant improvement in bladder symptoms was recorded at the 6-month follow-up (Fig. 2). Similarly, the improvement in the quality of life, measured by PFIQ, showed significant improvement from the first treatment, mainly in the bladder domain and not in the prolapse or bowel domains, and improvement was consistent and significant up to 12 months (Fig. 3).

The effect of the laser treatment on the tissue was demonstrated by the VHI score, showing significant improvement of the index at 6- and 12-month follow-up (Fig. 4). Similarly, vaginal biopsies at 6 months showed significant changes, as demonstrated in a menopausal patient in Figure 5. At baseline, the squamous epithelium appeared thin with 13–19 cell layers, and the junction between the basal surface of the epithelium and the connective tissue was flat with no connective tissue indentations into the epithelium. Six months after

TABLE 1. Demographic Characteristics of the Patients Who Completed 1-Year Follow-Up ($n = 42$)

Variable	Mean	SEM	Min	Max
Age (years)	49.1	1.5	32.0	73.0
Height (cm)	160.8	0.8	148.0	170.0
Weight (kg)	70.3	2.2	38.0	100.1
BMI (kg/m+)	27.1	0.8	15.0	37.2
Age of first period	12.7	0.2	9.0	17.5
Menopause age	49.1	1.2	39.0	55.0
Number of pregnancies	3.7	0.2	1.0	6.0
Number of births	2.7	0.2	0.0	5.0
Number of vaginal births	2.5	0.2	0.0	5.0
Number of Caesarian births	0.2	0.1	0.0	3.0
Number of assisted births	0.1	0.1	0.0	2.0
Maximal birth weight (Gr)	3461.6	76.4	2400.0	4300.0

Min, minimal value; Max, maximal value; SEM, standard error of mean.

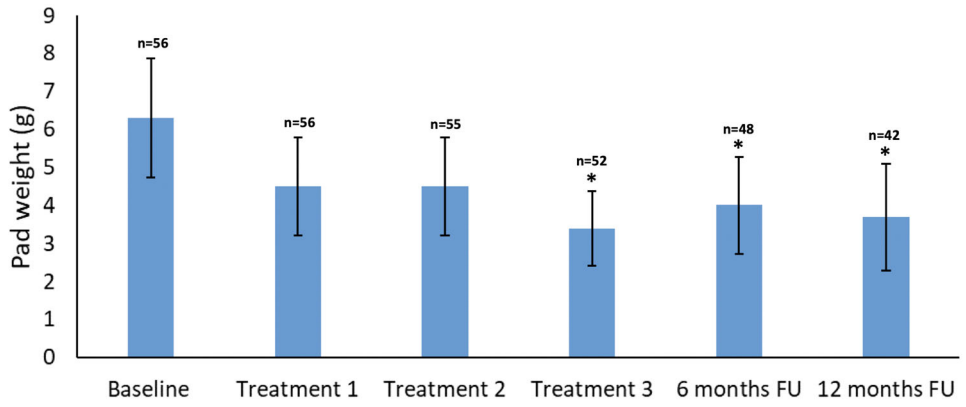

Fig. 1. Mean pad weight (g) ±SEM on the 1-hour pad test measured at baseline and different study time points. *$P < 0.05$ significantly different compared with baseline by paired t test. FU, follow-up. n, number of patients evaluated at each session; SEM, standard error of mean.

treatment, the squamous epithelium appeared much thicker, having between 24 and 42 cell layers. Numerous papillae of connective tissue projected into the epithelium, and therefore the junction between the basal surface of the epithelium and the connective tissue was not flat. The glycogen storage was increased and more blood vessels were seen in the connective tissue.

DISCUSSION

This study used a comprehensive subjective and objective assessment of vaginal CO_2 laser, including urodynamic tests, on patients with SUI for 1 year. Significant subjective improvement was consistent between 3 and 12 months, and 64.3% reported improvement at the 12-month follow-up (by PGI-I). Significant and consistent improvements were observed for 12 months in terms of subjective measures, including bladder symptoms measured by PFDI and condition-specific quality of life measured by PFIQ. Similarly, the significant improvement in objective measures lasted 12 months, as shown by 1-hour pad test. The urodynamic evaluation at 6 months demonstrated an objective cure in only 41.4% of patients. The laser effect on the vaginal tissue was consistent for 12 months, demonstrated by a significant improvement in the Vaginal Health Index or vaginal biopsies after 6 months. The vaginal CO_2 laser was found to be a safe treatment for patients with urodynamic proven stress incontinence, with mild side effects (mainly increased vaginal secretion).

Our results are similar to previously reported studies with Er:YAG laser, including that of Blaganje et al. [20], who reported that 21.4% (12/56) of laser group patients were dry 3 months after one session of treatment according to the ICIQ-UI SF (score = 0, means no leakage of urine by the scoring system), and Bizjak-Ogrinc et al. [21],

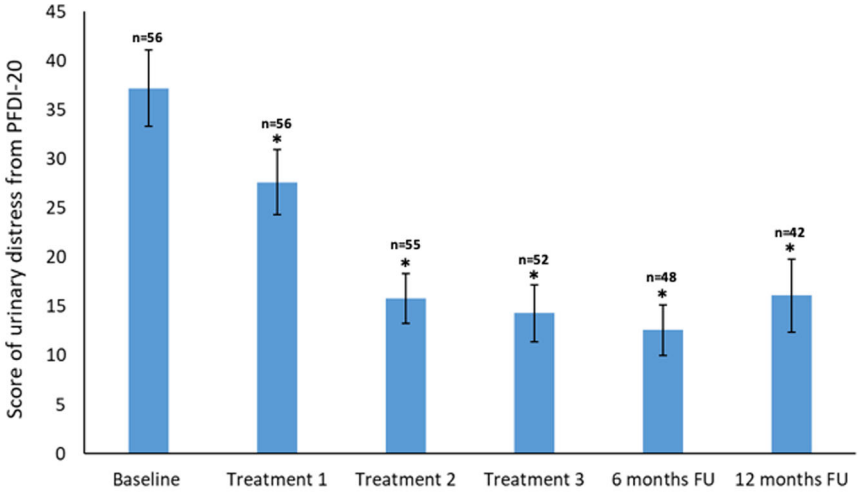

Fig. 2. Bladder symptoms as measured by the mean score ±SEM of urinary symptoms from the PFDI-20 (Pelvic Floor Distress Inventory-20) at baseline and different study time points. *$P < 0.05$ significantly different compared with baseline by paired t test. FU, follow-up; n, number of patients evaluated at each session; SEM, standard error of mean.

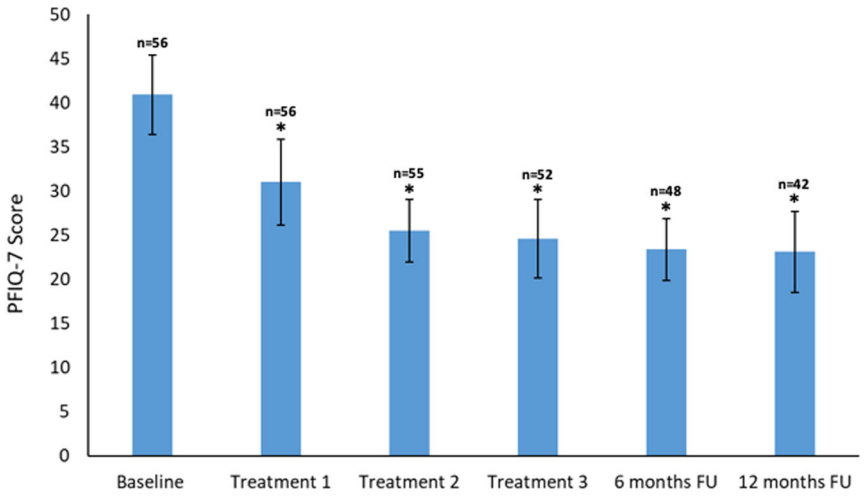

Fig. 3. Quality of life as measured by the mean score ±SEM of Pelvic Floor Impact on Quality of Life (PFIQ-7) at baseline and different study time points. $^*P < 0.05$ significantly different compared with baseline by paired t test. FU, follow-up; n, number of patients evaluated at each session; SEM, standard error of mean.

who showed that of 175 women with SUI or mixed incontinence, 60% reported no incontinence after two sessions and this had remained at the same level at the 12-month follow-up. On the contrary, Dabaja et al. [13] showed that vaginal CO_2 laser was less effective, and at 6 months, the values had returned to baseline.

Evaluation of new treatment modalities for SUI is complex and the Food and Drug Administration [22] recommends the inclusion of various objective and subjective evaluations based on well-accepted international outcome measures, as well as the inclusion of quality of life questionnaires. It is well-known that there is a wide variation in the "cure" rate, with some studies reporting 80.8% objective cure for incontinence with retropubic mid-urethral tapes (4), and others reporting 63% objective cure with the same surgical intervention. [23] There is also a wide spectrum of studies reporting subjective improvement following different surgical interventions, including a recent network meta-analysis by Imamura et al. [24], who graded the most effective interventions with an average probability of 97%, 76.1%, 67.7%, and 63.8%, for retropubic MUS, trans-obturator MUS, traditional sling, and open colposuspension, respectively.

Our subjective improvement of 64.3% following 1 year of treatment is comparable to some of the reported rates following surgery; however, the objective cure rate (41.4%) of vaginal CO_2 laser was inferior to surgical interventions. Based on our results, the vaginal CO_2 laser is a legitimate treatment modality in the armamentarium of SUI management and should be offered as an optional conservative treatment.

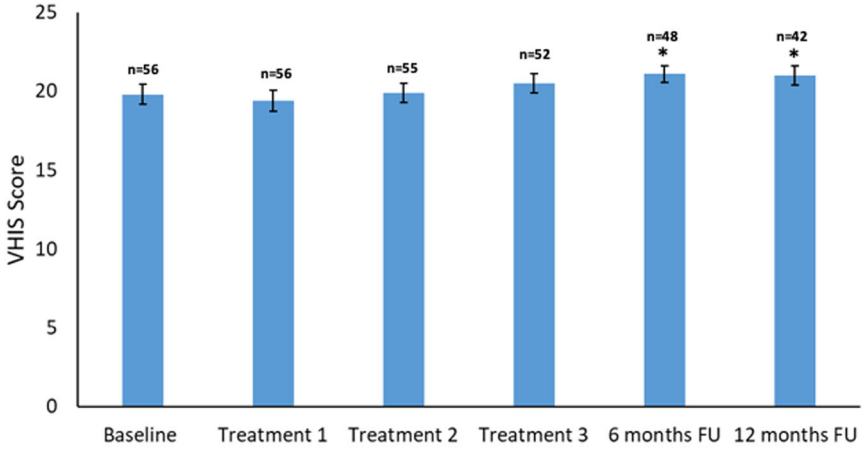

Fig. 4. Vaginal health index score (VHIS) measuring vaginal elasticity, fluid volume, pH, epithelial integrity, and moisture on a scale of 1–5. The mean score ±SEM is shown at baseline and follow-up visits. $^*P < 0.05$ significantly different compared with baseline by paired t test. FU, follow-up; n, number of patients evaluated at each session; SEM, standard error of mean.

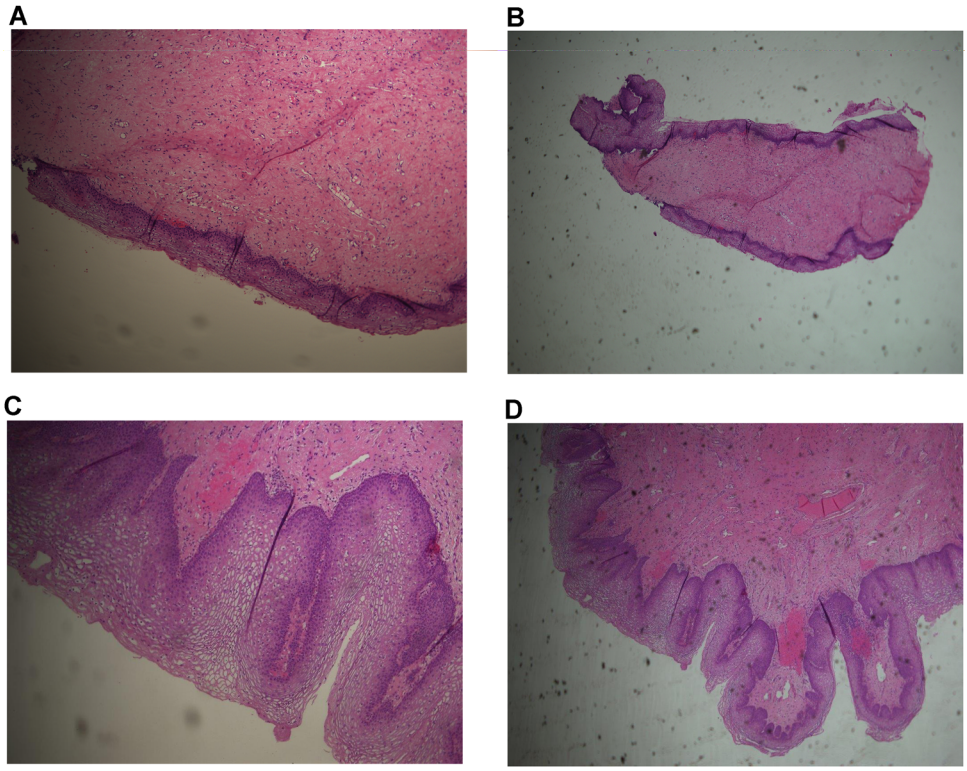

Fig. 5. Vaginal biopsies (H&E staining) at baseline at ×10 magnification (**A**) and ×4 magnification (**B**) and 6 months following fractional pixelated CO_2 laser treatment of the same patient at ×10 (**C**) and ×4 (**D**) magnifications. H&E, hematoxylin and eosin stain.

The vaginal CO_2 laser is known to affect the vaginal tissue, including the epithelium and lamina propria. The effects reported at 1 and 2 months in previous studies [25] were similar to those achieved in our study at 6 months. Though the effect of vaginal CO_2 laser on the tissue is well-documented, the mechanism of action on urinary incontinence is not clearly understood. Some authors have suggested that tissue laxity is changed by the heat of laser treatment, which may induce collagen denaturation, shorten collagen fibrils, and result in subsequent collagen remodeling and collagen neogenesis. These changes in collagen content might be the mechanism behind the improvements in this treatment, as it improves urethral support [10]. Others have reported changes in the vaginal muscular contractility by intravaginal pressure changes, and therefore, enhanced muscle strength might be a potential explanation [20].

The treatment protocol used in our study was performed according to the laser equipment manufacturer's instructions, and this was similar to protocols recommended by other laser manufacturers. However, the vaginal laser treatment of stress incontinence raises various questions such as the need to treat only the anterior vaginal wall, or the entire vaginal circumference (as we did in our study), the time interval that is needed between treatments, and the number of treatments. It is well-known that the trophic effect of laser on vaginal tissue is degraded over time, and therefore, to achieve a long-term effect, there is a need to perform periodic treatments. The study of González et al. [11] showed that additional yearly treatment could extend the clinical effect for 3 years. In a systemic review and meta-analysis, Pitsouni et al. [7] concluded that three treatment sessions are recommended in most treatment protocols, and Athanasiou et al. [26] showed that more than three treatments could achieve a better clinical effect than three treatments in menopausal women.

The recent consensus paper published by Alsheiek et al. [27] concluded that a short-term benefit could be achieved after a fractional laser, but most studies lack long-term follow-up and control groups. Our study differs from previous reports given its longer follow-up period of 12 months, and by the addition of well-accepted validated outcome measures, including subjective, objective, and histological parameters. However, the correlation between histological findings and clinical findings is beyond the scope of this study, and we are planning to study the different tissue changes and SUI parameters in the near future.

The limitations of our study were that this was not a comparative study between different treatment options, and there was a large number of dropout patients (10 of 52) during the study follow-up, mainly due to patient compliance. As we are aware of this limitation, we also analyzed all the patients that had at least one treatment ($n = 56$). No differences were found between this group and

the group who completed the 12 months follow-up. We cannot assume that those who were lost to follow-up at 12 months showed no improvement in SUI. However, the strength of our study is its prospective longitudinal design and its inclusion of a wide variety of outcome measures that provide a comprehensive impression of treatment efficacy over 1 year. Our study showed sustained subjective improvement (64.3%) in incontinence at 12 months, similar to the improvement rate of 77% at 12 months reported by Ogrinc et al. [20]. On the contrary, Dabaja et al. [12] showed recurrence of symptoms to levels similar to baseline at 6 months posttreatment.

CONCLUSION

The need for an ambulatory alternative treatment for SUI is increasing, as the safety of mesh implants has come under scrutiny owing to reports of women experiencing severe complications [5,6]. The growing international controversy around vaginal mesh has led to litigation against manufacturers worldwide, forcing the withdrawal of some products [6]. The spectrum of treatments for stress incontinence ranges from a conservative approach with pelvic floor exercises or incontinence pessaries to surgical treatment such as mid-urethral tapes or retropubic procedures. The efficacy increases from 50% in the conservative options to 86% in the surgical treatments. We think that vaginal laser treatment can be an optional treatment in cases that failed pelvic floor exercises or incontinence pessaries, and before surgical intervention. In this medical situation, and based on our results, we suggest that more studies should evaluate vaginal laser treatment as an optional treatment for SUI, and more specifically, comparative studies with pelvic floor exercises and other ambulatory treatments are needed.

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