Efficacy of Fractional CO_2 Laser in the Treatment of Genitourinary Syndrome of Menopause in Latin-American Population: First Peruvian Experience

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Objective: This PUBA study aimed to assess the efficacy of fractional CO2 laser in the treatment of genitourinary syndrome of menopause (GSM).
Methods: GSM symptoms were assessed before, 1 month after the first session and 1 month after the third session of laser (3 sessions with a 30 days interval between them) in 60 women (median, interquartile range: 55, 49–69). Subjective (visual analog scale) and objective (Vaginal Health Index, VHIS; Vaginal Maturity Index/Frost Index; Spanish Overactive Bladder Questionnaire-Short Form, USMEX Spanish OAB-qSF and Female Sexual Function Index, FSFI) measures were used during the study period to assess CO2 fractionated laser treatment outcomes compared to baseline.
Results: Fractional CO_2 laser treatment was effective to improve GSM symptoms (vaginal dryness, vaginal itching, vaginal burning, dyspaurenia, dysuria, urinary urgency; $P < 0.001$) after three sessions, as well as VHIS (median, interquartile range: 13, 10–15 at baseline vs. 21, 20–23 at the fourth month follow up; $P < 0.001$), Frost Index (median, interquartile range: 28, 24–31 at baseline vs. 8, 6–10 at the fourth month follow up; $P < 0.001$), USMEX (median, interquartile range: 56, 46–68 at baseline vs 14, 13–16 at the fourth month follow up: $P < 0{,}001$) and FSFI (median, interquartile range: 5, 2–14 at baseline vs 30, 28–32).
Conclusions: In this sample, the data suggests that fractionated CO2 laser is an effective alternative for GSM treatment with positive outcomes that persists over time. Lasers Surg. Med. © 2019 Wiley Periodicals, Inc.

Key words: quasi-experimental study; menopause; laser Gas; genitourinary syndrome of menopause; dyspareunia

INTRODUCTION

Menopause has been associated with numerous changes that involves all organs in the female body, specially the urogenital organs [1,2]. Symptoms appears as disturbances of the urogenital tract (vaginal irritation, itching, burning, dryness, dyspareunia, and urinary complications).

The Genitourinary Syndrome of Menopause (GSM) is defined by the *International Society for the Study of Women's Sexual Health* (ISSWSH) and the *Board of Trustees of The North American Menopause Society* (NAMS) in 2013 as a new terminology used to describe symptoms that occur secondary to vulvovaginal atrophy (VVA). This new terminology is of sum importance given that, in many opportunities, it is under-diagnosed by trained physicians [3,4].

This syndrome is associated to the loss of estrogen production. The genital tract is sensible to low levels of this hormone, and more than half of post-menopausic women experiences the symptoms related to this, affecting their sexual function and quality of life. This changes tend to worsen overtime and needs specific treatment [5,6]. First line treatment for this condition is hormone replacement therapy (HRT) with topical estrogen, but a new tendency to use CO_2 fractionated laser has appeared as an option for patients with contraindications or discomfort to HRT [7].

The CO_2 fractionated laser (CO2FL) stimulates the production of collagen, hyaluronic acid, fibroblasts, and proteoglycans through heat shock proteins. This has been discovered that enables the revitalization of vaginal mucosa without the risks from proper hormonal replacement therapy [8–15].

Currently there is evidence about the efficacy and use of the CO_2 fractionated laser in the treatment of Genitourinary Syndrome of Menopause. *Pitsouni* and collaborators

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published in 2017 a systematic review of 14 studies in which they concluded that it can reduce the severity of symptoms, improve the quality of life of post-menopausic women and recover the state of the vaginal mucosa. Nevertheless, the quality of the research was low or very low. Based on published evidence, the use of fractionated CO_2 laser is still controversial in the treatment of GSM [7].

The purpose of this study was to determine the efficacy of laser therapy in postmenopausal patients with GSM measuring symptoms outcomes, quality of life, pH changes, and Frost maturity index.

MATERIALS AND METHODS

Study Design

A PUBA: Prospective Uncontrolled Before (the initiation of the laser-therapy) and After (the last laser-therapy) study was conducted in patients at the Centro de Cirugía Femenina Laser CIRUFEME, Lima-Perú, between June of 2014 and May of 2017.

Selection of Participants

Female patients that gathered the following conditions were included: 1 year of amenorrhea as a minimum, no previous Hormonal Replacement Therapy (HRT), with symptoms of vulvovaginal atrophy, with changes at the vaginal mucosa related to hipoestrogenism confirmed by a trained physician, and that are willing to take part in questionnaires and the study.

Female patients with the following conditions were excluded: vaginal prolapse greater than II grade by the POPQ classification (*Pelvic Organ Prolapse Quantification System*), that has undergone pelvic floor surgeries or surgeries with mesh placement, active urogenital infections, smokers and with a BMI $< 26\,kg/m^2$.

Laser Dispositive

We used the CO2 Microablative SmartXide Touch V^2LR Laser (MonaLisa Touch®, FI, Italy) fabricated in 2014 with the following settings: "*Dot power* 40 watt," permanence time of 1000 miliseconds and "Dot spacing 1000 um." $2.68\,Jl/cm^2$ fluence was utilized. The procedure with the *MonaLisa Touch Laser* has already been performed with the parameters previously described [16]. These parameters were chosen based on data obtained from studies of vaginal wall ex vivo species, where remodeling of the connective tissue without damage of the annexed tissues was demonstrated [10].

Procedures And Methods For Measuring Variables

The patients received 3 sessions of CO2 Laser in a fractional manner. It was delivered in two stages, first at the level of the vaginal canal, and then at the vestibular level, at an interval of 30 days. All the procedures were performed after topical analgesia. After the treatment, no additional estrogenic medication was prescribed, nor analgesic, only sexual, and exercise restriction for 1 week.

The sociodemographic characteristics of the study sample were collected before the start of the study. In addition, the inclusion/exclusion criteria were verified before starting with the first laser application.

The primary outcome measure was Visual Analog Scale (VAS) change in 10 categories of symptoms commonly associated with VVA. Secondary outcomes included Female Sexual Function Index, Gloria Bachmann's Vaginal Health Index, Frost Index (Hormone Maturation), and USMEX Spanish OAB-qSF.

The VAS measured 10 categories of symptoms commonly associated with the urogenital syndrome of menopause: vaginal dryness, vaginal itching, vaginal burning, dyspareunia, vaginal discharge, dysuria, frequency, urgency, and nocturia. The VAS was measured on a scale of 11 points for each symptom, with 0 being the lowest level (nonexistent) and 10 the highest (extreme). The use of EVA in this type of scenario was previously reported in studies of vulvovaginal atrophy [16,17]. A baseline measurement was made prior to treatment, 1 month after treatment and at the fourth month after the last session. In addition, the participants filled the Female Sexual Function Index (FSFI) before the intervention and at the end of the first intervention cycle. A questionnaire of 19 topics developed as a brief, multidimensional, self-reported instrument to assess key elements in the sexual function of women [18]. It allows to have scores of individual domains in a scale of five points (desire, excitement, lubrication, orgasm, satisfaction, and pain) and a total score of the scale from 2 to 36. This questionnaire has already been used in randomized clinical studies to investigate sexual function [19] and has been validated to Spanish in a Colombian population [20].

The effect of treatment on the female genitourinary tract was evaluated using Gloria Bachmann's Vaginal Health Index before the intervention and at the end of the intervention cycle. This consists of five parameters: elasticity, fluid volume, pH, epithelial integrity and humidity. Each parameter has a score of 1 (worst condition) to 5 (best condition) [21].

Urinary urgency was assessed using the USMEX Spanish Overactive Bladder Questionnaire-Short Form (Spanish OAB – qSF). It has 19 topics, it is self-assessed and a specific instrument to evaluate symptoms (six topics) and quality of life [1] in patients with overactive bladder. This questionnaire has already been validated for its use in Spanish [22].

The Frost Maturity Index was used to evaluate the hormonal status. It consists of selecting five fields randomly ($\times 10$ magnification) and count 100 epithelial cells in each area determining the percentage of superficial, intermediate, and parabasal cells. The result is expressed as MI = % parabasal cells:% intermediate cells:% superficial cells. An MI of 90: 10: 0 in women was considered as menopause (predominance of basal cells) [23].

Sample Size

All patients who underwent laser therapy within the study period were recruited.

No patients that were treated for GSM at the clinic during the study period declined laser therapy.

The sample consisted of 60 patients total.

Cost of the Procedure

Patients paid 1000 USD for all three sessions and all patients paid the same amount.

Statistical Analysis

Frequencies and percentages were presented for the quantitative and median variables and interquartile ranges for the continuous variables according to the results of the normality tests (Shapiro-Wilk, meaning a value of $P < 0.05$). U-mann Whitney was used for continuous non-parametric variables. The data were processed in the statistical software STATA version 14.

RESULTS

A total of 60 women were included for the analysis. The median age of patients were 55 years (interquartile range: 49–69), with a median onset of menopause at 48 years old (interquartile range: 45–51). They had a median parity of 2 (interquartile range: 1–3). Patients were weighted with a median BMI of 24 (interquartile range: 20–25). (Table 1 shows the patients baseline characteristics and clinical-cytological improvement).

There were changes in vaginal symptoms after 1 month of treatment and at the fourth month, evidencing improvements from the first month of treatment above 60%

TABLE 1. Patients Baseline Characteristics and Clinical-Cytological Improvement

	First visit	1 month	*P*	4 months	*P*
Vulvovaginal atrophy (score)					
Vaginal dryness: median (interquartile range)	9 (8–10)	4 (3–5.5)	0.0001	1 (0–2)	0.0001
Vaginal itching: median (interquartile range)	6 (4–8)	0 (0–2)	0.0001	0 (0–0)	0.0001
Vaginal burning: median (interquartile range)	8 (5–9)	1.5 (0–3)	0.0001	0 (0–1)	0.0001
Dyspareunia:median (interquartile range)	8 (5–10)	4 (2–5)	0.0001	0 (0–0)	0.0001
Vaginal discharge: median (interquartile range)	3 (2–5.5)	1 (0–2)	0.0001	0 (0–0)	0.0001
Dysuria: median (interquartile range)	5.5 (3–7)	0 (0–2)	0.0001	0 (0-0)	0.0001
Frequency: median (interquartile range)	6.5 (4–8)	2 (1–4)	0.0001	0 (0–0)	0.0001
Urgency: median (interquartile range)	8 (6–9)	1 (0–2.5)	0.0001	0 (0–0)	0.0001
Nocturia: median (interquartile range)	5 (3.5–7)	0 (0–1)	0.0001	0 (0–0)	0.0001
Sexual Function(Score)					
FSF: median (interquartile range)	5 (2–14)	ND	NA	30 (28–32)	0.0001
Vaginal Mucosa					
Bachmann's score: median (interquartile range)	13 (10–15)	ND	NA	21 (20–23)	0.0001
Vaginal Ph: median (interquartile range)	6.8 (6–7.2)	ND	NA	6 (5.5–6.2)	0.0001
Cytology(cell percentage)					
Presence of parabasal cells: median (interquartile range)	90 (70–100)	ND	NA	0 (0–10)	0.0001
Presence of superficial cells: median (interquartile range)	0 (0–0)	ND	NA	20 (10–30)	0.0001
VMI/FROST index: median (interquartile range)	28 (24–31)	ND	NA	8 (6–10)	0.0001
Hyperactive Bladder (Score)					
USMEX-SF: median (interquartile range)	56 (46–68)	ND	NA	8 (6–10)	0.0001

FSF, Female Sexual Function; VMI, Vaginal Maturation index/FROST index; USMEX-SF, Spanish overactive bladder questionnaire-short form.

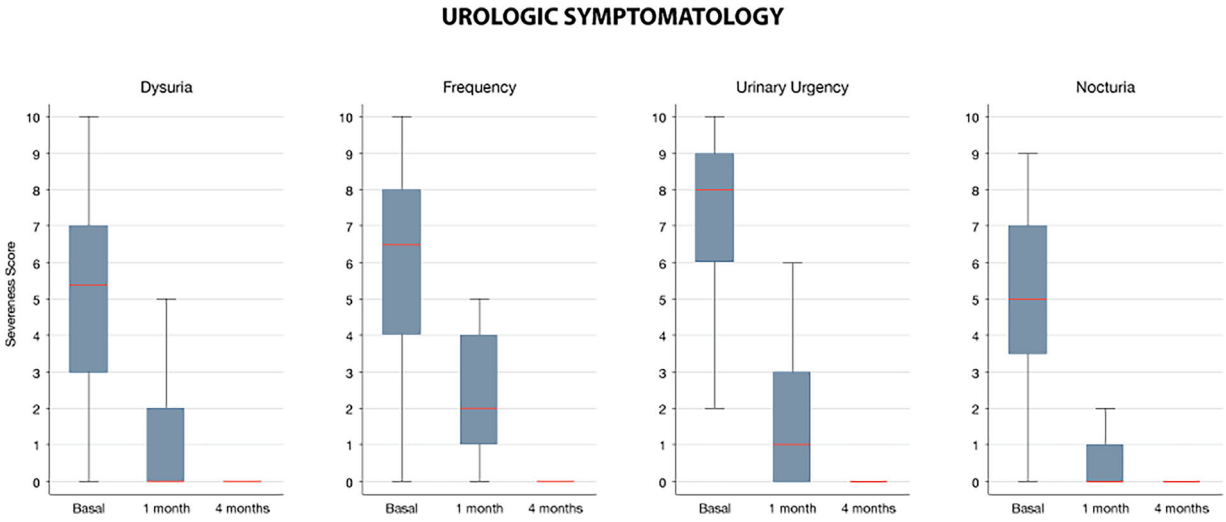

Fig. 1. Vaginal symptomatology.

according to the VAS (Visual Analogue Scale), to reach almost 100% finished the treatment cycle. The main symptoms of consultation were vaginal dryness, as well as dyspareunia (Figure 1).

Improvements in the symptoms due to hyperactive hypoestrogenic bladder were shown, evaluated by the VAS (Visual Analogue Scale), basically focused on urinary urgency, frequency and nocturia. Improvements in this area were much faster and with better impact for patients in their quality of life, reaching 100% finished treatment (Figure 2).

In Figure 3: A, B; the vaginal mucosa was evaluated, by means of the 5 Bachman Score parameters (elasticity, fluidity, Ph, epithelial mucosa, hydration), showing changes in the characteristics of the vaginal mucosa, from an initial score from 13 on average at the beginning, to 21 at the fourth month of control. The vaginal pH on average before the placement of fractionated CO_2 laser was 6.8, and after that, it decreased to 6.

Female sexual function was evaluated with the FSFI and its six domains (desire, excitement, lubrication, orgasm, satisfaction, pain). Starting with a score of 5, reaching to 30 at 4 months of treatment, and having as a maximum score 36 as the sum of all its domains. We can also mention that vaginal dryness, as well as dyspareunia, could cause an inhibitory effect on desire and excitement, that is why when improving these two, improvement is also observed in the other domains (Figure 4).

Figure 5 shows the presence of hormonal activity, through the maturation of parabasal cells, even superficial ones. At the beginning the predominance of parabasal cells

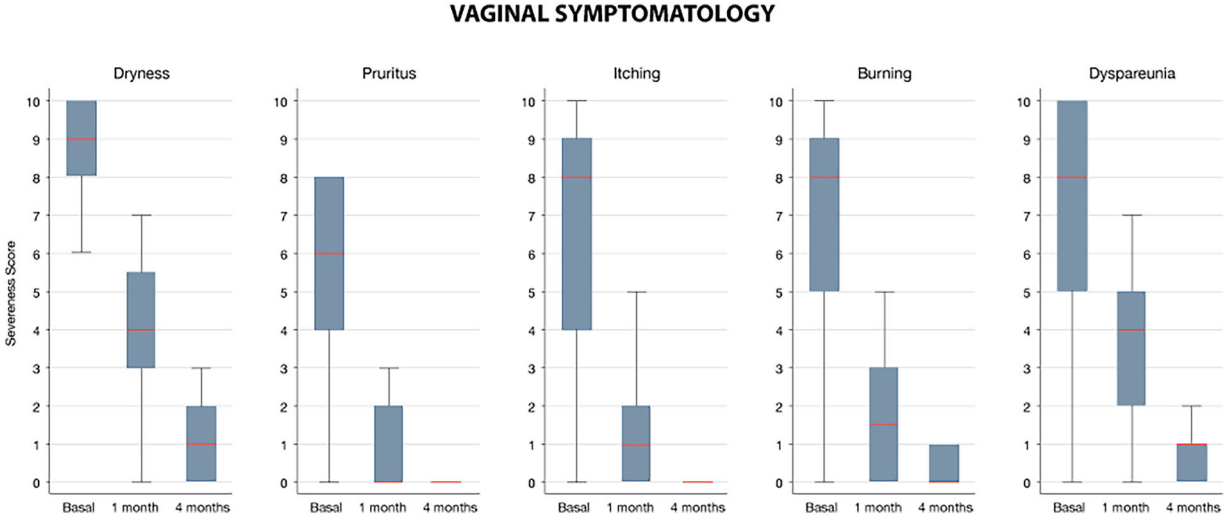

Fig. 2. Urologic symptomatology.

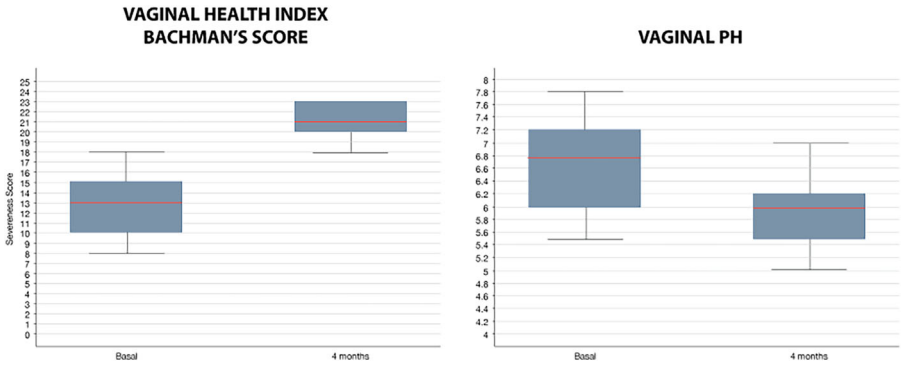

Fig. 3. A (Bachmans Score) and B (Vaginal Ph).

was around 90%, with the superficial ones almost nil. While the three laser sessions were being completed, and after the end of the fourth month, we can observe the decrease in the percentage of basal levels, and at the same time the intermediate and superficial cells were increasing, showing again hormonal activity at the level of the vaginal epithelium.

As for complications during the study period, only one patient presented dysuria and urinary frequency. She had a negative U/A and urinary culture. She was managed with phenazopyridine without complications.

DISCUSSION

The SmartXide Touch V2LR Microablative CO2 laser has recently been introduced to improve the symptoms of GSM and thus avoid the potential adverse effects of other types of therapy, especially hormonal therapy [16,24].

There is more than one type of laser, such as erbium [14]. The erbium laser has thermal properties, while the one used in our study has thermal and ablative properties, stimulating heat shock proteins, growth factors, production of collagen, and hyaluronate acid; resulting in tissue rejuvenation [8–15,25]. This technology is applied in the vagina to obtain a regeneration of the epithelium with a minimally invasive procedure, improving the elasticity and hydration of the vaginal walls and thus relieving the uncomfortable symptoms of menopause. Approximately 15% of pre-menopausal women, 40–60% of post-menopausal women and 10–20% of women receiving systemic hormone therapy experience urogenital atrophy [26–28]. In the AGATA multicenter study, based on 913 patients, all women diagnosed with GSM suffered from vaginal dryness; 77.8% reported dyspareunia; while burning, itching and dysuria occurred in 56.9%, 56.6% and 36.1%, respectively [29]. These symptoms significantly decrease the quality of life of patients, especially in the sexual sphere, and are the basis of the treatment.

The fractionated CO_2 laser, with an appropriate selection of wavelength and frequency of laser pulses, can radiate deep layers of the vagina producing an increase in the synthesis of collagen and angiogenesis. These changes lead to restore the trophism of the vaginal tissue without trauma to superficial and adnexal tissues.

Salvatore et al. and Perino et al. published studies that demonstrated satisfaction with the procedure as well as improvement in the patient's symptoms in 2014 and 2013,

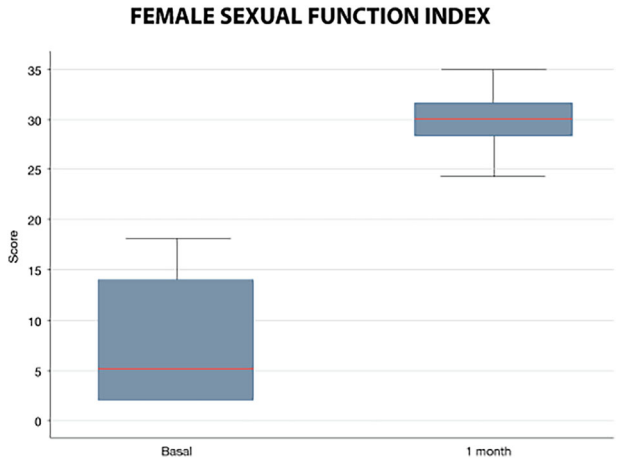

Fig. 4. Female Sexual Function Index (FSFI).

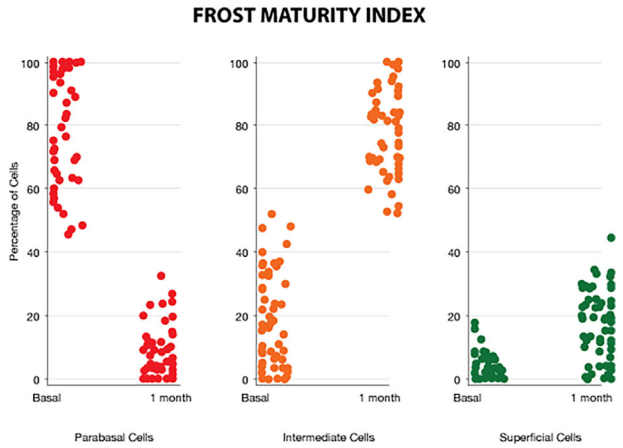

Fig. 5. Frost Maturity Index.

respectively. They studied around 50 post-menopausal women each. A significant improvement in quality of life and of all the symptoms studied were reported when compared with the basal status of the patients. Over 80% of patients were satisfied or very satisfied with the procedure. No adverse effects were evidenced [16,26].

Safety and efficacy constitute a major part involving any new treatment or procedure, thus the relevance of studies that supports its use. In 2016, Eric et al. evaluated the safety and efficacy of fractionated CO_2 laser in vulvovaginal atrophy. Twenty-seven post-menopausal women were studied with a significant improvement in all symptoms of vulvovaginal atrophy. Before the second and third sessions, 86.6% reported that they felt better or much better than in previous sessions and 96% reported that they were satisfied or extremely satisfied during the follow-up. The data suggests that the laser is effective and safe for the treatment of vaginal vulvar atrophy [17].

Regarding the negative impact on the quality of life and sexual function of women, Salvatore et al. also investigated the beneficial effects of laser in postmenopausal women. Seventy-seven patients with symptoms of vulvovaginal atrophy were included and treated with three sessions of fractionated laser. Sexual function and quality of life were evaluated before treatment and after 4 weeks of follow-up, evidencing a significant improvement. A total of 17 (85%) of 20 women who were not sexually active due to the severity of the symptoms resumed a normal sex life at 4 weeks of the last session [17]. Likewise, Vera et al. conducted a randomized, placebo-controlled, double-blind clinical trial in 2015 comparing the results of three controlled groups (45 patients divided into 3 groups of 15): Co2 fractionated laser, topical estrogen, and the combination of both for postmenopausal patients with symptoms of vulvovaginal atrophy. In contrast to the previous study, the laser-only arm demonstrated an increase in pain in the Sexual Function Index, but an improvement in dyspareunia in the EVA [30]. It is difficult to explain the incongruence of pain results in two studies where the same laser and parameters were used, but some differences are that in the latter study only two sessions of treatment were performed and that the first was not controlled by placebo. More randomized, double-blind, placebo-controlled clinical trials should be conducted in order to have more consistent information.

In the present study, the first done in peruvian population, we found evidence that suggests that fractionated CO_2 laser in treatment of genitourinary syndrome of menopause is highly effective in reducing symptomatology and improving quality of life. Symptoms decreased with each laser therapy reaching almost nil by the end of the treatment cycle, as shown in Table 1, Figures 1 and 2. Besides symptomatology, Figure 5 shows objective evidence of a recovery in hormonal activity at the level of the vaginal epithelium by the maturation of parabasal cells. By the end of the first month there was a marked decrease in them while the intermediate and superficial cells increased significantly.

Given the lack of randomization, placebo-control, power analysis, and not having blinded the workers to avoid the expectation of them as a possible confusing result, the data must be interpreted with care; however, the improvement of the GSM symptoms were highly significant. Another limitation of this study would be the lack of funds to continue with the Frost Maturity Index in all of our patients at fourth month after baseline.

An important factor to take into consideration is the cost of this new laser therapy. Lang et al. assessed patient's satisfaction and out-of-pocket expense for the fractional CO_2 laser (SmartXide). The study showed that the vast majority of patients reported being satisfied with both costs and treatment results. Another important aspect was that satisfaction with the out-of-pocket expense did not correlate with household income [31]. As far as this results are encouraging, it is still impossible to perceive how this therapy will be received in the context of a country with scarce resources like ours. Further research should adopt this thinking and compare the satisfaction and cost associated with the continuous use of vaginal estrogen vs fractionated laser in the same period of time, thus assessing cost-effectiveness.

Some of the strengths of this study include the prospective design and the use of defined objective and subjective criteria despite the limitations. The results of this study were encouraging, with a notable perception of the effectiveness of fractionated laser treatment even after a single session.

CONCLUSION

Fractionated CO_2 Laser is an effective alternative for Genitourinary Syndrome of Menopause with good outcomes even after a single session and in the short term follow-up. This therapy should be taking into consideration as an effective alternative for patients in which hormonal therapy is contraindicated.

HUMAN STUDY AND INFORMED CONSENT STATEMENT

The present study has been carried out in accordance with The Code of Ethics of the World Medical Association (Dlecaration of Helsinki) for experiments involving humans. The institutional ethics committee from Clinica de Urologia Avazanda Urozen, Lima, Perú evaluated and approved the study. Informed consent was obtained for experimentation with human subjects prior to the beginning of the study.

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