SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PH.D.)

Investigation of the effects of vaginal microablative fractional CO_2 laser treatment

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The PhD defense will be held on 21 October, 2020. at 1 p.m.

Live online access will be provided via Webex. If you wish to join the discussion, please send an e-mail to the sipos.attila.gergely@med.unideb.hu address until 12 p.m. at latest on the previous day of the defense (October 20, 2020). For technical reasons, after the deadline, it will not be possible to join the defense.

1. INTRODUCTION AND AIMS

In the past few decades, the use of laser therapy become popular in medicine. Amongst other indications such as dermatology, ophthalmology, and general surgery, the gynecological application became the focus of interest. In 2014 the US Food and Drug Administration (FDA) approved laser therapy for certain gynecological procedures. Consequently, the number of publications investigating the beneficial effect of vaginal laser treatment in women with vulvovaginal atrophy and related conditions increased significantly. Genitourinary syndrome of menopause (GSM) includes the hypoestrogenic changes to the vulvovaginal and bladder-urethral areas that occur in menopausal women. The syndrome with its bothersome symptoms affects more than 50% of postmenopausal women and negatively influences their quality of life. Based on the common pathophysiology, this condition results not only in vulvovaginal atrophy, but it affects the integrity of the pelvic floor. Next to non-hormonal and hormonal therapeutic options, most recently, vaginal laser treatment was found to be a safe and efficient treatment modality for women with GSM, although the FDA does not yet approve this form of therapy.

Our studies aimed to investigate different aspects of the effect of vaginal microablative CO_2 laser treatment. We have determined that GSM's signs and symptoms (objectively evaluated by healthcare providers and subjectively reported by patients) improve after laser treatment. We have attempted to find the best possible combination of questionnaires available for evaluating the results of intravaginal CO_2 laser on pelvic floor complaints, and we have also examined the possible relationship between vaginal cytology and vaginal dryness after laser treatment.

We hope that our results add to the existing literature, and help better understand the role of vaginal CO_2 laser treatment as a new therapeutic modality of GSM.

2. MATERIALS AND METHODS

2.1. Patients

Patients were enrolled in our prospective cohort studies at the outpatient urogynecology clinic of the Department of Obstetrics and Gynecology, University of Debrecen, Hungary, between March 2017 and September 2018. We enrolled postmenopausal women with the presence of any of the following symptoms: vaginal dryness, feeling of vaginal itching, burning, or any other classic GSM/VVA symptoms. Moreover, criteria included mild stress (SUI), or urge urinary incontinence (UI), vaginal looseness due to diminished pelvic muscle tone, or symptoms of low grade (≤Stage II) pelvic organ prolapse (POP), according to the pelvic organ prolapse quantification system (POP-Q). We defined postmenopausal, as the patients had at least 12 consecutive months of amenorrhea without any other clear reason or elevated follicle-stimulating hormone (FSH) blood levels of 30mIU/ml or higher. Exclusion criteria were pregnancy, any kind of hormone therapy (local or systemic) in the last two years, vaginal infection at presentation, cytological atypia, dysmenorrhea, POP >Stage II, severe UI, severe fecal incontinence (FI) or any disease, which would interfere with the study protocol. Patients were also asked to discontinue the vaginal use of any non-hormonal or other products at least six weeks before the intravaginal laser therapy. At the first visit, a general gynecological examination was performed, and detailed medical history was taken (age, body mass index, previous deliveries or operations, menstruation cycle, the onset of menopause, hormonal therapy).

Our studies were approved by the Hungarian National Institutional Review Medical Research Council (ETT TUKEB 18504-1/2017/EKU). All the enrolled patients signed written informed consent before participating in the research. There were no withdrawals or discontinuation of treatment due to adverse events.

2.2. Laser therapy

For treating the vaginal mucosa microablative, fractional CO_2 laser system (SmartXide2V 2 LR; Deka, Florence, Italy) was applied, with a specific 360° probe, especially for intravaginal procedures. During the treatment, laser beams were fractionally ejected in really small areas (DOT's) around the vaginal wall. According to scientific literature, the laser was used in D-Pulse mode. Depth was set, laser power, dwell time, and spacing was adjusted: SmartStak 1, 30 W power, 1,000 μs dwell time and 1,000 μm spacing. Laser treatment was performed in three sessions, 4-6 weeks apart.

2.3. Assessment of vaginal condition

Vaginal health index (VHI) is an objective scale to assess the vaginal condition, with scoring for vaginal moisture, vaginal fluid volume, vaginal elasticity, vaginal pH, and vaginal epithelial integrity on a scale of 1 to 5. The summary score of VHI can vary between 5 and 25, and lower the score indicates greater atrophy. VHI scores were completed before each treatment and four weeks after the final treatment of intravaginal CO_2 laser.

As an objective measurement visual analog scale (VAS) was used to assess subjective complaints such as vaginal pain, vaginal dryness, itching, burning, dyspareunia, dysuria. The VAS score can pick up values on a scale of 1 to 10, depends on the severity of individual symptoms. A lower score indicates fewer symptoms.

2.4. Vaginal cytology

Vaginal cells for smear samples were collected during gynecological examination with scraping movements from the middle third of the lateral vaginal wall with a spatula. In every specimen, 200 cells were analyzed by an independent board-certified cytopathologist blinded to the clinical information. Evaluating the smears first parabasal (P), intermediary (I), and superficial (S) cell counts were defined, then these values were multiplied by 0, 0.5, and 1.0, respectively. The sum of these three values comprises the vaginal maturation value (VMV) of

Meisels and an increased percentage of P cells, and I cells suggests a decreased estrogen effect. According to scientific data, VMV values ranging from 0 to 49 indicate low estrogen effect, 50 to 64 moderate, and 65 to 100 indicate high estrogen levels in the vaginal epithelium. During our research in 3 sessions of intravaginal CO2 laser treatment, four weeks apart vaginal smear was performed in the following time points: after the first treatment as baseline; after the first and second treatment and 4-6 weeks after the third laser treatment.

2.5. Questionnaires

Standardized and validated questionnaires were aiming to demonstrate the subjective pelvic floor symptoms of the examined patients. Assessing pelvic floor conditions, there are several questionnaires available in the literature. For our study, we have selected the short-form version of the Pelvic Floor Distress Inventory (PFDI-20). In previous studies, this item was found valid, reliable, and responsive to clinically important changes. The PFDI-20 has three components: Pelvic Organ Prolapse Distress Inventory 6 (POPDI-6), Colorectal-Anal Distress Inventory 8 (CRADI-8), and Urinary Distress Inventory (UDI-6). In POPDI-6, there are pelvic organ prolapse related questions. The CRADI-8 contains information about colorectal-anal distress of patients, and UDI-6 has questions concerning urinary distress. To specify the presence or absence of pelvic floor distress symptoms the patients find response options: 0 refers to no symptoms, and a scale ranged from 1 (“not at all” as “symptoms are present but not bothersome at all”) to 4 (“quite a bit” as in symptoms greatly bothersome). To calculate the score, the mean score of answers within each component is multiplied by 25 to obtain the scale score (range 0–100). Summary scores are calculated by summing the scale scores (range 0–300). Higher scores indicate more bothersome symptoms and distress.

2.6. Statistical analysis

To describe clinical and demographic characteristics for continuous variables, mean and standard deviation (SD) was used; in the case of categorical variables, frequencies, and percentages were reported.

VHI and VAS scores were analyzed with Microsoft Excel 2013 software (Microsoft Corporation, Redmond, WA, USA). To compare the before and after cores, we applied paired Student's t-test. Differences were considered significant when the $P < 0.05$.

For statistical analysis of the data obtained from the questionnaires, SigmaStat/ SPSS (SPSS Inc., Chicago, IL) software was used. Wilcoxon rank-sum test was used to compare the differences between the baseline scores and scores following each treatment. Differences were considered significant when the $P < 0.05$.

The sample characteristics of the vaginal cytology study were compared between premenopausal and postmenopausal patients with Student's t-test. The change of vaginal maturation value (VMV) scores and vaginal dryness resulting from CO_2 laser treatment over time were analyzed using a mixed model approach because data was collected repeatedly at three different time points. The reported means, standard errors, and P-values have been adjusted based on within-group and between-group interactions, just like the potential for skewed distributions between variables. For data analysis SAS 9.4 statistical software (SAS Institute Inc., Cary, NC, USA) was used, we set the risk of Type I error at $\alpha=0.05$. To estimate sample size, a power analysis was performed, which resulted in ideally 52 participants.

3. RESULTS

3.1. Results of the short-term efficacy of vaginal CO_2 laser therapy

We have included 51 women in our study with the mean age of 57,0 ± 9,9 years. 72 % of the study participants (37 women) were in menopause. The average number of deliveries in their anamnesis was 1,9 ± 0,9. We have encountered no adverse event related to the study protocol. The baseline score of VHI was 14,0 ± 4,9, which increased after every consecutive intravaginal CO_2 laser treatment (mean± SD, 15,0 ± 4,7 after the first, 18,2 ± 4,6 after the second and 19,5 ± 4,9 after the third treatment). We detected significantly improved VHI scores after every treatment compared whit baseline scores and compared whit each consecutive treatment scores as well.

The mean baseline score of VAS in this study was 15,6 ± 14,1, which decreased to 9,0 ± 10,8 after the firs, 5,9 ± 9,2, after the second and 3,4 ± 7,5 after the third intravaginal laser therapy. There was a significant improvement in VHI scores after every treatment compared whit baseline scores and compared whit each consecutive treatment scores as well.

3.2. The effect of vaginal CO_2 laser treatment on pelvic floor dysfunction symptoms based on the PFDI-20 questionnaire

We enrolled forty menopausal women with GSM symptoms in our study. The mean age was 58 ± 10 years. The summary scores of PFDI-20 showed no significant improvement after the first treatment compared to baseline scores (mean ± SD score, 74 ± 47 at baseline vs. 57 ± 38 after the first treatment, p =0,1). After the second and third treatment, there were significantly lower summary scores (46 ± 38, $p < 0,01$ and 44 ± 39, $p < 0,01$) as it was at baseline.

After the evaluation of each individual domain of the PFDI-20 questionnaire, we found the followings:

There was no significant change in POPDI-6 standardized scores according to prolapse symptoms after the first treatment (mean ± SD score, 21 ± 18 at baseline vs. 17 ± 15 after the first treatment, p=0,44). However, after the second treatment, we found a significant improvement in the standardized score to 14 ± 15 (p=0,03). After the third treatment, we detected further improvement in the questionnaire mean scores (13 ± 13, p=0,01).

UDI-6 was used to estimate the severity of the urinary distress symptoms. This domain showed no significant difference after the first treatment of vaginal CO_2 laser (mean ± SD score, 36 ± 25 vs. 29 ± 23 after the first treatment, p =0,36). However, after the second and third treatments our patients had significantly improved standardized scores of 24 ± 20 (p= 0,03) and 22 ± 21 (p= 0,01).

CRADI-8 standardized scores account for the colorectal-anal symptoms of the included patients. The mean scores of this domain did not change significantly during three vaginal laser treatments (mean ± SD score, 16 ± 16 vs. 12 ± 13 after the first treatment, 11 ±12 after the second treatment, 10 ± 14 after the third treatment).

3.3. The effect of vaginal CO_2 laser treatment on vaginal cytology

We enrolled 52 women in our study; 34 of the patients were in menopause. Compared with the premenopausal group, participants in the postmenopausal group were significantly older (mean ± SD, 63 ±6 vs. 46 ± 6 years, p <0,01). At baseline, postmenopausal women had significantly lower VMV scores than premenopausal women (mean ± SD, 42 ± 23 vs. 68 ± 13, p <0,01). The VAS for vaginal dryness was higher (more bothersome symptoms) in postmenopausal women compared with the premenopausal group (mean ± SD, 5,7 ± 4 vs. 2,4

± 3, p< 0,01). Evaluating all of the patients, we found a weak negative significant correlation between VMV and vaginal dryness VAS (r =−0.282, p<0,01). There was no significant change in VMV during vaginal laser therapy. However, the VAS scores of vaginal dryness improved significantly (lower value) after each treatment. The vaginal dryness VAS improved significantly (lower VAS value) from baseline in the premenopausal as well as the postmenopausal group after the three treatments of vaginal CO_2 laser (postmenopausal 5,7 ± 4 vs. 1,6 ± 2,5, p<0,01 and premenopausal 2,4 ± 3 vs. 0,2 ± 0,5, p<0,01). Those participants in whom we found improvement in VMV scores (higher VMV during the treatment) had significantly lower (less symptom) dryness VAS compared with women without an improvement in VMV after the three vaginal laser therapy (mean ± SD, 0,3 ± 0,8 vs. 1,6 ± 2,6, p=0,04). Summarizing the VAS scores for vaginal dryness we found significantly lower dryness values in both groups (improvement in VMV vs. no-improvement in VMV) after the three treatments compared with baseline (mean ± SD, 0,3 ± 0,8 vs. 4,0 ± 3,6, p<0,01 and 1,6 ± 2,6 vs. 4,6 ± 4,0, p<0,01).

4. DISCUSSION

During their life, at least half of the female population becomes affected by the bothersome symptoms of vulvovaginal atrophy (VVA). These genitourinary changes are a response to the decreased level of circulating estrogen caused by aging. In developed countries such as Hungary, the prevalence of conditions caused by low estrogen production is rapidly increasing and has a significant adverse effect on the health-related quality of life of peri- and postmenopausal women.

According to the International Society for the Study of Women's Sexual Health and the North American Menopause Society, genitourinary syndrome of menopause (GSM) is the the new term for the previously used vulvovaginal atrophy (VVA), while it describes more accurate the changes of the genital area, lower urinary tract, and sexual function.

GSM is a chronic, progressive condition, the syndrome or its features manifest in some manner in approximately 40-54% of postmenopausal women. The management varies according to symptom severity. First-line therapy contains local non-hormonal (lubricants, moisturizers) and hormonal products, in severe cases, systemic hormone replacement therapy (HRT), or selective estrogen receptor modulators (SERMs) can be offered. Most recently, vaginal laser treatment was introduced as a new option for women with GSM, even though the FDA has not yet approved this method for this indication.

Fractional CO_2 laser is widely used in dermatology and cosmetology. This form of therapy proved to be safe and efficient by inducing tissue remodeling resulting in the rejuvenation of the skin. Similar changes are detectable in vaginal tissue after CO_2 laser treatment. As a result of the thermal effect of the laser beam first collagen denaturation and tissue shrinking occurs, then rapid regeneration begins with the synthesis of new extracellular matrix (ECM) components and epithelial proliferation. Fractional CO_2 laser rejuvenation can

be delivered with a variety of microbeam sizes and densities to achieve the required effect without the thermal damage of the surrounding tissue.

In our prospective cohort studies, we aimed to investigate different aspects of the effect of vaginal microablative CO_2 laser treatment. It was found that signs and symptoms of GSM, as objectively evaluated by health care providers and subjectively reported by patients, improve after treatment.

The effect of vaginal laser therapy can manifest in the improvement of various GSM symptoms. Based on previous publications, laser treatment was performed in 3 sessions 4-6 weeks apart. The VHI includes scoring of vaginal moisture, vaginal fluid volume, vaginal elasticity, vaginal pH, and vaginal epithelial integrity on a scale of 1 (poorest) to 5 (best). A lower score indicates greater atrophy. The improvement of VHI scores was significant after each laser treatment. Participants reported the intensity of their most common symptoms, such as vaginal pain and dryness, itching, burning, dyspareunia, and dysuria using a visual analog scale (VAS). The scale's left extremity refers to no present symptoms (0), and the right extremity refers to the worst possible symptom (10). VAS scores were significantly decreased after every treatment; the total improvement inVAS was 78% compared to baseline, which correlates with other studies investigating the effect of vaginal laser treatment.

Based on its pathophysiology, genitourinary syndrome of menopause results not only in vulvovaginal atrophy, but it affects the integrity of the pelvic floor as well. The hypoestrogenic environment leads to significant tissue changes such as loss of collagen, elastin, and smooth muscle in the pelvic floor. These effects may develop pelvic floor dysfunctions (PFDI), like pelvic organ prolapse (POP), urinary, and defecatory distress. We aimed to find the best possible combination of questionnaires available to evaluate the results of intravaginal CO_2

laser on pelvic floor dysfunctions. Out of the several questionnaires available, we have selected the short-form version of the Pelvic Floor Distress Inventory-20 (PFDI-20). PFDI-20, with its subquestionnaires, covers broad symptoms of PFD by including lower urinary tract and urinary incontinence symptoms, symptoms related to prolapse, and colorectal-anal dysfunction or fecal incontinence. After two treatments, the urinary symptoms on the UDI-6 domain of the questionnaire improved significantly. There was also a significant improvement in the prolapse related answers (POPDI-6) after more than one laser session. CRADI-8 colorectal scores improved after every laser session, even though the results were not statistically significant.

The relationship between vaginal cytology and vaginal dryness after CO_2 laser treatment was also examined. Pre- and postmenopausal women were included in our study. Vaginal dryness VAS improved significantly in both study groups. We were surprised to find no significant changes in vaginal cytology after vaginal CO_2 treatment. Previous publications concerning vaginal laser treatment revealed significant changes in vaginal cytology and significant improvement in vaginal dryness. In a study by Pitsouni et al., 53 postmenopausal women with moderate to severe GSM symptoms were treated with three sessions of vaginal CO_2 laser, and significant improvement was found in VMV. At the baseline, none of the participants had VMV > 49, but at the 12-weeks follow-up, 57% of the participants had VMV > 49. In our study, the mean baseline VMV was >49. A VMV of <49 indicates a low estrogenic, atrophic vaginal environment. Similar to our findings, the participants in Pitsouni's study that could not overpass the threshold of VMV > 49 still had improved GSM symptoms. Based on these prior findings and our results, it seems that vaginal CO_2 laser treatment improves vaginal dryness, whether it alters vaginal cytology or not. Our research was different from previous studies because the baseline of VMV was above the threshold for a low estrogenic state based on vaginal cytology (VMV < 49) regardless of the fact that our postmenopausal patients were on average in menopause for 14 years. We can assume that women with very low

VMV respond differently to laser treatment than women with values near or above the threshold levels. These findings indicate that improvement in vaginal dryness might not be only the result of changes in vaginal cytology and a healthier vaginal epithelium, but other factors might contribute to the improved GSM symptoms.

We believe that our studies' strength is that our findings in accordance with previous publications bring added value to the existing literature about the effects of vaginal fractional CO_2 laser treatment. Our research's primary limitation is the relatively small sample size of the study population, the lack of a control or sham group, and a short follow-up period. To assess the treatment efficacy of vaginal lasers on genitourinary and pelvic floor symptoms more accurately, a randomized, sham-controlled (laser vs. sham laser) trial would be necessary.

The use of vaginal laser for various urogynegological indications is controversial. Despite the numerous publications on vaginal laser treatment, there is no reliable long-term, randomized, placebo, or drug and sham-controlled trials (RCT). These circumstances inspired the FDA warning in 2018, about the lack of evidence of vaginal laser safety.

The bothersome symptoms caused by menopausal vulvovaginal atrophy have a significant adverse impact on the quality of life of peri- and postmenopausal women. The vaginal laser became popular as a potential treatment option for GSM, but even more evidence required regarding its safety. Our research aimed to add to the existing pieces of evidence.

5. SUMMARY OF MAJOR RESULTS AND SCIENTIFIC NOVELTIES

- To the best of our knowledge, we are the first research team to investigate the effects of vaginal CO_2 laser treatment on the pelvic floor using the PFDI-20 questionnaire.

- Our findings suggest that vaginal microablative CO_2 laser treatment significantly improved postmenopausal pelvic floor dysfunction-related urinary and prolapse symptoms measured with the selected questionnaire.

- To achieve the beneficial effect of vaginal laser treatment, only one treatment is not enough, and at least two sessions of vaginal CO_2 laser treatment is necessary.

- Based on our findings, vaginal dryness improved despite no change in vaginal cytology. Vaginal dryness, as a symptom, has probably multiple underlying etiology, not just an epithelial abnormality.

- The improvement in symptoms by laser treatment suggests that affecting the deeper, submucosal layer of the vaginal tissue is critical in achieving the best results and not just affecting the mucosa.

6. PUBLICATIONS

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Candidate: Attila Gergely Sipos
Neptun ID: IQLPD9
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. Takács, P., **Sipos, A. G.**, Kozma, B., Cunningham, T. D., Larson, K., Lampé, R., Póka, R.: The Effect of Vaginal Microablative Fractional CO2 Laser Treatment on Vaginal Cytology.
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Magyar Nőorv. Lap. 82 (2), 56-61, 2019.

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Total IF of journals (publications related to the dissertation): 6,04

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

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