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FEMALE UROLOGY (L COX, SECTION EDITOR)

Laser Therapy for Genitourinary Syndrome of Menopause

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Abstract

Purpose of Review The purpose of this article is to review the available data regarding the application and therapeutic outcomes of laser therapy for the treatment of genitourinary syndrome of menopause (GSM).

Recent Findings There have been several studies regarding the use of laser therapy for the treatment of GSM. Most of these studies show a trend toward safe and effective treatment in the short term (less than or equal to 12 weeks). However, these studies are lacking in randomization, blinding, placebo, and comparison groups.

Summary Although laser therapy for the treatment of the symptoms of GSM appears promising, there is currently a lack of high-level and long-term evidence regarding its safety and efficacy. There is also a lack of professional guidelines in the USA regarding this modality of treatment, specifically for GSM. Opportunities exist for future research in this area, specifically to determine safety and long-term outcomes of therapy.

Keywords Genitourinary syndrome of menopause · Vulvovaginal atrophy · Laser therapy · Microablative fractional CO_2 laser · Erbium:YAG laser · Postmenopausal urinary incontinence

Introduction

Genitourinary syndrome of menopause (GSM), previously referred to as vulvovaginal atrophy (VVA), is an array of vaginal symptoms associated with the loss of circulating estrogen in the transition to menopause [1]. Menopause is the permanent cessation of menstruation, which is associated with a decline in circulating estrogen levels coincidental with the loss of ovarian activity. Symptoms associated with menopause can be classified into two groups: vasomotor (hot flushes) and vaginal. The symptoms of GSM involve the vagina, vulva, and urologic tissues. Vulvovaginal symptoms include vaginal pain, dyspareunia, dryness, itching, and tissue friability. Urologic symptoms include urinary frequency, urgency, incontinence, hematuria, and recurrent urinary tract infections [1]. Gross architectural changes to the external and internal female genitalia can be evident on physical examination evidenced by regression and thinning of the labia minora, retraction of the introitus, and prominence of the urethral meatus [2]. Tissue changes are also evident on a microscopic level including thinned stratified squamous epithelium, decreased glycogen stores in epithelial cells, and loss of vascularity and dermal papillae [3].

GSM is thought to affect up to 50% of women undergoing the menopausal transition [4]. Although symptoms can have a significant negative impact on sexual function and quality of life, it has been reported that only 20% of women affected by GSM will discuss these symptoms with a physician [5]. Traditionally, these symptoms have been treated with either non-hormonal or hormonal therapies. Non-hormonal therapies include water or silicone-based vaginal lubricants, vaginal moisturizers, herbal remedies and soy products, and estrogen agonists and antagonists. Currently, the only FDA-approved non-hormonal treatment option for GSM is ospemifene, a selective estrogen receptor modulator, which has been shown to be effective and safe in short-term usage. However, it does carry a concern for possible development of estrogenic effects on endometrial tissue and has been linked to systemic side

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effects including hot flushes [6]. The use of radiofrequency ablation of vaginal epithelium is currently being investigated as a non-hormonal treatment option [1]. FDA-approved hormonal therapies include both local and systemic applications of estrogen and progestin.

Laser therapy has been introduced as a non-hormonal option for the treatment of GSM. This therapy works by stimulating the use of the body's own repair mechanism to repair, grow, and heal tissues [2]. These microscopic tissue changes are thought to lead to tissue regeneration. There are different types of lasers currently being used in medicine, with their applications determined by the specific properties of the laser and the tissue on which the therapy is to be performed. Some of these variables include gain medium, wavelength, wattage, water absorption, and depth of penetration. Laser energy can also be delivered either as a continuous wave or intermittently, known as fractional (or pulsed). One of the benefits of fractional therapy is decreased damage to deeper or surrounding tissues [7].

The two types of lasers that have been most thoroughly investigated for the treatment of GSM are the microablative CO_2 laser and the erbium:YAG (Er:YAG) laser. The CO_2 laser is currently considered the gold standard in dermatologic surgery for the treatment of skin and mucosal lesions [8]. It uses a gas medium at a wavelength of 10,600 nm. This wavelength is strongly absorbed by water, resulting in various depths of penetration and ablation depending on the water content of the tissue. The CO_2 laser has a small diameter beam that is typically applied in a non-continuous fashion with both of these variables intended to limit the amount of deep thermal damage [7]. Er:YAG lasers have been traditionally used for dermatologic and dental procedures. This laser uses a solid medium and has a wavelength of 2940 nm, close to the peak absorption of water. This correlates to an increased affinity of the laser for water molecules, which allows for more focused ablation and deeper secondary thermal effects [9]. Also, Er:YAG lasers do not have coagulative properties like those of the fractional CO_2 laser, which in theory leads to a higher chance of bleeding with treatment [7]. Although the two lasers differ in characteristics and functionality, the ultimate result is thought to be collagen remodeling, leading to tissue restructuring and rejuvenation [10].

Treatment for GSM with either the CO_2 laser or the erbium:YAG laser typically consists of three procedures spaced 4–6 weeks apart, as this was the treatment scheme described in the original pilot study by Salvatore et al. in 2014 [11]. A probe is inserted into the vagina, emitting laser energy 90° in four directions. The probe is withdrawn and rotated circumferentially until the entire vaginal wall is treated. Each laser session lasts approximately 5–10 min, does not require anesthesia, and is performed on an outpatient basis [9].

Microablative Fractional CO_2 Laser Therapy

The microablative fractional CO_2 laser system has become the most widely used laser therapy for the treatment of GSM. The effects of fractional CO_2 laser therapy on postmenopausal vaginal tissue have been investigated and demonstrated at the microscopic level. Zerbinati et al. performed a histologic comparison of postmenopausal non-estrogenized vaginal wall biopsies before and after a 12-week treatment period with fractional CO_2 laser therapy. The biopsies were examined under light and electron microscopy. Treatment with the fractional CO_2 laser resulted in restoration of the vaginal epithelium with ultrastructural findings similar to a premenopausal state that included thickened stratified squamous epithelium with increased collagen support, increased glycogen in epithelial cells, increased fibroblasts, increased vascularity, and presence of sub-epithelial papillae. These findings reflect those found in similar histologic studies of skin undergoing laser therapy for other conditions [3].

Athanasiou et al. investigated the changes in vaginal flora of postmenopausal women undergoing microablative fractional CO_2 laser therapy. Postmenopausal women commonly suffer from a basic vaginal pH due to abnormal amounts of pathologic bacteria, which can lead to an increased risk of developing urinary tract infections [12]. In this study, the authors observed increased amounts of *Lactobacillus* and other premenopausal vaginal flora following laser therapy, which led to a decrease in vaginal fluid pH. Because of these findings, they concluded that vaginal health could be improved with microablative fractional laser therapy treatments [12].

Salvatore et al. were the first to study the use of fractionated CO_2 laser in postmenopausal women for the treatment of GSM in 2014. Their initial prospective pilot clinical study is out of Italy, and included 50 women with VVA who were treated with intravaginal fractionated CO_2 laser therapy. Their primary endpoint was to assess feasibility and efficacy of fractional CO_2 laser therapy in the treatment of GSM in postmenopausal women. Inclusion criteria included age greater than 50 years, at least 12 months postmenopausal, symptoms of VVA, and dissatisfaction with or lack of response to local estrogen therapies. Exclusion criteria were prior use of systemic hormone therapy within 6 months of study, recent use of local therapy, recent urinary tract or genital infections, significant pelvic organ prolapse, or prior pelvic surgeries. Treatment in the study consisted of three intravaginal laser applications in an outpatient setting at 4 weeks apart, over a 12-week period. Results of the treatment were assessed using the Vaginal Health Index Score (VHI), which assigned an objective value for vaginal tissue observations, and a visual analog scale (VAS) to assess symptom severity. The VHI and VAS assessments were performed both pretreatment and after each of the three laser treatments during the 12-week period. In addition, study participants were asked to rate the level of

pain associated with the procedure and overall satisfaction at the end of the treatment period.

VHI scores for the participants improved with each subsequent fractional CO_2 laser treatment. Additionally, the subjective symptoms of GSM all improved with each treatment based on the VAS results. Posttreatment, 84% of women reported being very satisfied or satisfied, 14% uncertain, and 2% very dissatisfied. No adverse events were noted during the study. The authors' primary conclusion was that laser therapy for the treatment of GSM was feasible, effective, and safe. They acknowledge limitations including a small cohort, short study length, and lack of long-term follow-up. Most importantly, there was no placebo or control group. It should also be noted that the patients selected for this study were included only if they were dissatisfied with prior treatment modalities, not just exposure to prior treatments alone [11].

Salvatore et al. then published an extension to the study in 2015 to investigate changes in sexual function after fractional microablative CO_2 laser therapy. The same inclusion criteria and treatment strategy were employed on a new cohort of postmenopausal women for this study. Sexual function was reported both before and after treatment using the Female Sexual Function Index (FSFI) and a VAS for overall satisfaction with sexual life. Quality of life before and after treatment was also reported using a similar VAS.

Out of 77 patients recruited to the study, 75 were enrolled and completed treatment. Two patients could not complete treatment due to vaginal anatomy that was not compatible with the laser probe. Of the 77 women recruited, only 57 were sexually active prior to the study with the remaining 20 reporting abstinence due to the severity of their GSM and associated symptoms. Treatment with laser therapy allowed 17 of 20 women who were not sexually active prior to therapy to engage in sexual intercourse following treatment. The remaining 3 women had persistent symptoms of GSM and had not participated in sexual activity at the time of the 12-week follow-up. It is unclear if these 3 women included the two that did not undergo treatment. Patients who were sexually active at the end of the follow-up period showed a significant improvement in FSFI score. Significant improvements were also seen in overall satisfaction with sexual life, symptoms of GSM, and quality of life.

Based on these findings, the authors suggested that sexual function and satisfaction with sexual life could be improved by treatment of GSM with microablative CO_2 laser therapy. Similar limitations exist for this study including small cohort, short investigative period, no long-term follow-up, and lack of a control group. It is important to note that their results regarding sexual function only included the patients that were sexually active. There is no information reported regarding the outcomes of the 3 patients who had persistent symptoms after treatment and were unable to become sexually active. It is also unclear if these 3 patients were included in the data regarding GSM symptoms and quality of life. They also note a likely high incidence of confounding factors regarding sexual activity in the patients due to lack of randomization and an inability to ensure that the participants did not use any vaginal or other therapies, like pelvic floor physical therapy, to enhance sexual intercourse during the study [13].

In 2016, Sokol et al. published the first pilot study in the USA investigating the safety and efficacy of the fractional CO_2 laser for the treatment of GSM. Using similar inclusion and exclusion criteria as the initial pilot study by Salvatore et al. in 2014, the authors were able to enroll 30 participants. The study was also structured in the same fashion as the Italian pilot study with regard to laser settings, treatment schedule, duration of the study, and scoring metrics. At the 12-week follow-up point, 3/30 patients (10%) had been lost to follow-up. The authors reported statistically significant improvement in symptoms of GSM, vaginal health, sexual function, and quality of life based on changes in VAS and VHI scores and improvements in FSFI. Of the remaining participants at 12-week follow-up, 96% reported being very satisfied or satisfied with their treatment. Again, limitations including small cohort, short follow-up, and lack of a control group were noted in this study as well. This study included 30% fewer participants compared to the initial pilot study by Salvatore and colleagues 2 years prior. They also reported a secondary outcome regarding vaginal elasticity. This was measured by the size of the dilator the vagina could accommodate at the initial visit compared to subsequent treatment visits. They noted that 83% of participants had an increase in dilator size without discomfort from baseline at a subsequent follow-up visit [14].

In July 2017, Sokol et al. published updated results, which included results at 1-year follow-up. Of the 27 remaining participants after the 3-month follow-up, 24 women returned for follow-up at 1 year. At this point, 92% of participants were still either very satisfied or satisfied with their treatment. Statistically significant improvements in all symptoms except dysuria were noted. There was not a statistically significant difference in the results obtained at 3 months and 1 year for the primary outcomes. Comparing the 3-month results, a lower proportion of participants were found to have improved vaginal elasticity. The authors concluded that laser therapy had a beneficial effect on the symptoms for GSM at 1 year. They did note that 2 patients had mild to moderate pain during therapy and 2 had bleeding complications. Limitations to this study again are small cohort, lack of a control group, and lack of a comparison therapy [15].

Behnia-Willison et al. published data assessing long-term outcomes (up to 24 months) of fractional CO_2 laser therapy for GSM. Inclusion criteria for this study were less strict, requiring patients to meet the age requirement of 51–86 years of age, be postmenopausal, and have at least one bothersome symptom of GSM. Exclusion criteria were similar to prior studies. A validated pelvic floor questionnaire (The Australian Pelvic

Floor Questionnaire) was used to gauge pre- and posttreatment symptoms, which differs from the VAS and VHI scores used in prior studies. Colposcopy and biopsies were also performed pretreatment to stage and confirm vaginal atrophy. Time intervals evaluated in this study were pretreatment, conclusion of treatment (12 weeks), and at 1–2 years posttreatment. The authors reported statistically significant improvement in symptoms of GSM and sexual function at the 1–2 years follow-up. One important limitation to this study was high attrition rates at the 12–24 months follow-up. There was also no control group for this study [16].

While most studies have looked primarily at the vulvovaginal symptoms related to GSM, several studies have also investigated results specifically pertaining to pelvic floor dysfunction and urologic issues including recurrent urinary tract infections, overactive bladder (OAB), and incontinence. Behnia-Willison et al. noted secondary outcomes in their study that included improvements in vaginal prolapse, bladder function, and urgency incontinence [16]. Perino et al. published preliminary results in 2016 regarding the use of fractional CO_2 laser therapy for the treatment of OAB. Thirty patients with both GSM and OAB underwent three rounds of laser therapy, with at least 30-day intervals between treatments. Outcomes regarding improvement in GSM symptoms and OAB symptoms were measured using visual analog scales, questionnaires, and micturition diaries. They found statistically significant reductions in the frequency of micturition and urgency episodes per day after the three laser therapy treatments. They also reported a significant decrease in the number of episodes of urge incontinence for the subgroups of patients with this condition. They again confirmed improvement in symptoms related to GSM [17].

Also in 2016, Pitsouni et al. published a study regarding the use of microablative fractional CO_2 laser therapy for GSM symptoms. This study also evaluated changes in urologic symptoms including frequency, urgency, and incontinence. They used several questionnaires to assess treatment outcomes including the Urogenital Distress Inventory, the King's Health Questionnaire, and those by the International Consultation on Incontinence. They found significant improvement in lower urinary tract symptoms (LUTS) among patients and concluded that CO_2 laser therapy may be an effective treatment for LUTS associated with GSM [18].

Gonzalez Isaza et al. published a pilot study in May 2017 using fractionated CO_2 laser therapy as treatment for stress urinary incontinence (SUI) in patients with GSM. The study showed improvements in SUI based on questionnaire results and improvement in 1-h pad weights. However, this study has similar limitations to those of the prior studies including non-randomization of participants, small population, and lack of a control group. They make the statement that laser therapy could be considered in patients with GSM and mild SUI who do not have an indication for surgical intervention for their SUI [19]. This treatment could be promising given the relative lack of non-surgical options for the treatment of SUI currently; however, higher quality data is needed to make this recommendation.

Erbium:YAG Laser

While a majority of published data regarding laser therapy for GSM has used the fractional CO_2 laser system, other types of medical lasers have been investigated as well. The Er:YAG laser is used for dermatologic and dental procedures but has also been studied as a potential treatment for the symptoms of GSM. Several studies have been published that evaluate its use in patients with GSM.

Gambacciani et al. published a prospective, longitudinal pilot study in 2015 that looked at the effects of the vaginal erbium laser (VEL) in the treatment of GSM among postmenopausal women. They evaluated 45 patients before and after treatment of their symptoms of GSM with VEL using similar subjective and objective measures as studies of fractional CO_2 laser therapy, a VAS for symptom evaluation, and the VHI for objective evaluation of vaginal changes. A control group was incorporated into the study, consisting of 25 women who underwent treatment with standard therapy for GSM (topical hormonal agent applied to vaginal epithelium) and were followed for the same time period. The authors report that women undergoing VEL and standard therapy had similar improvement in symptoms and VHI score within the initial 12-week treatment period but that women who underwent VEL showed continued improvement in symptoms at 6 months while those treated with standard therapy had some regression of improvement. They concluded that VEL leads to significant improvement in symptoms of GSM. They also report several secondary outcomes, one being improvement in SUI after treatment with VEL. This was hypothesized to be due to vaginal tightening induced by the treatment. They also report that a group of women in the VEL treatment group who had never been treated with hormonal therapy did improve with VEL therapy and they therefore proposed that VEL as primary treatment for GSM could provide an opportunity for women in which hormonal therapy is contraindicated, such as women with a history of breast cancer or hypercoagulability. Limitations to this study include lack of randomization of patients between treatment options and small treatment populations [20]. In a later review published in 2017, Gambacciani et al. also noted improvement in pelvic organ prolapse with VEL treatment [10].

In 2017, Gaspar et al. published a study comparing treatment of the symptoms of GSM with Er:YAG laser compared to topical estriol. Fifty postmenopausal women were divided into two groups: an active control group who received the

topical estriol treatment, and the laser treatment group, who underwent standard Er:YAG laser therapy. Each group was treated over an 8-week period and participants were followed for up to 18 months for continued evaluation of symptoms. Biopsies of vaginal tissue were obtained before, during, and after treatment for histologic analysis and subjective information regarding symptoms was obtained from patients at the same time intervals via the visual analog scale. They found a statistically significant improvement in symptoms in the laser treatment group and report that this improvement was more pronounced than that seen in the active control group. It should be noted that at the 6-month follow-up both treatment groups showed a statistically significant improvement in symptoms. When looking at 12- and 18-month follow-ups, there continued to be statistically significant improvements in symptoms for patients in the laser therapy group while the improvements were no longer statistically significant for the active control group, leading to the conclusion that VEL is more durable than traditional topical therapy. Histologically, they found changes in the vaginal epithelium and lamina propria consistent with improvement in quality and health of the tissue in both treatment groups. They did note however that these histologic improvements were present at the later follow-up time interval more often in patients who had undergone laser therapy. Clear limitations to the study are lack of randomization of patients to either the control or laser therapy groups and small treatment group sizes [21].

Professional Guidelines

The American College of Obstetrics and Gynecology published a Position Statement in May 2016 with the purpose of advising obstetrician-gynecologists in the USA in this innovative technology. The statement reiterated that the FDA has not approved CO_2 laser therapy for the treatment of VVA. They recognize that preliminary observational data has shown potential benefits in the treatment of VVA, however they cite a need to further assess efficacy, safety, and long-term benefits. They emphasize that for any emerging therapy, it is critical to counsel patient comprehensively regarding their options [22].

Neither the American Urological Association nor the European Association of Urology has released a position statement regarding the use of laser therapy for the treatment of GSM.

Conclusions

A review of the literature suggests that laser therapy is a promising treatment option for postmenopausal women with GSM. However, the studies largely lack randomization, blinding, placebo groups, and comparison groups. The majority of data is reported in short-term studies and, although these studies seem to indicate safety and efficacy, longer-term studies are needed. For postmenopausal women with GSM who have contraindications to hormonal therapy such as breast cancer, laser therapy is a promising option. While improvements in vulvovaginal symptoms have been widely reported, there is still limited data regarding changes in urologic symptoms. Areas of future research may include investigating the effects of laser therapy on bothersome lower urinary tract symptoms including frequency and urgency, the incidence of recurrent urinary tract infections, and rates of stress urinary incontinence in patients with GSM. Additional data from more rigorous clinical trials is clearly needed to further assess the efficacy and safety of this procedure in treating GSM in all patients. A search of ClinicalTrials.gov with the keywords "vaginal laser" and "vaginal atrophy" showed 10 trials pertaining to the use of laser therapy for the treatment of GSM, VVA, or SUI. These studies will hopefully provide the necessary higher-level evidence to support the efficacy of laser therapy for the treatment of GSM.

Compliance with Ethical Standards

Conflict of Interest Andrew Rabley, Tina O'Shea, Russell Terry, Sharon Byun, and M. Louis Moy each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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