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CLINICAL OPINION

Laser therapy as a treatment modality for genitourinary syndrome of menopause: a critical appraisal of evidence

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Abstract Interest in laser therapy as a nonhormonal option for the treatment of genitourinary syndrome of menopause (GSM) has increased. We conducted a systematic review of the use of laser therapy for the relief of GSM symptoms. Six electronic databases were searched and conference abstracts were searched manually from the introduction of laser therapy to the present date. The keywords used were: "genitourinary syndrome", "vulvovaginal atrophy", "postmenopausal symptoms", "laser therapy" and "fractional laser treatment". Of the 165 articles identified in the search, none was a randomized controlled trial. As a result, we included three observational studies without a control group and one case–control study that met our inclusion criteria. The total number of women included in the four studies was 220. The collated data suggest that laser therapy may be valuable as a nonhormonal therapeutic modality in the management of GSM. Higher quality of evidence from randomized controlled trials is required to establish the efficacy of laser treatment in the management of GSM.

Keywords Genitourinary syndrome · Vulvovaginal atrophy · Atrophic vaginitis · Postmenopausal symptoms · Laser therapy · Fractional laser treatment

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Introduction

Genitourinary syndrome of menopause (GSM) is characterized by symptoms such as vaginal dryness, dyspareunia, irritation, urinary incontinence, and urinary tract infections. GSM replaces the previous term vulvovaginal atrophy as agreed upon by a joint terminology conference sponsored by the North American Menopause Society and the International Society for the Study of Women's Sexual Health [1]. GSM is a common condition that can significantly affect quality of life and sexual function. Several therapeutic options are available to alleviate the symptoms including hormonal and nonhormonal products [2]. There are approximately 15 laser companies in the market, the majority providing products based on the CO_2 and Er:YAG lasers. The CO_2 laser with a wavelength of 10,600 nm and the Er:YAG laser with a wavelength of 2,940 nm (mid-infrared) are the most widely used lasers in the skin rejuvenation field, and interest in the use of these lasers as a nonhormonal option for the treatment of GSM has recently increased [3]. We conducted a systematic review of laser therapy as a treatment modality for the relief of symptoms of GSM.

Materials and methods

Using the PRISMA guidelines, the rapid appraisal of the literature was based on the following questions:

1. What will happen if we do not offer this treatment modality? (Prognosis).
2. Is there evidence to show this intervention helps? (Treatment Benefit).
3. Are there any harms reported as a result of the intervention? (Treatment Harm).

Six electronic databases and the internet were searched without language restrictions from the introduction of laser therapy to the present date. Relevant publications and websites included Cochrane, PUBMED (Medline), EMBASE, CINAHL plus, OneSearch and Google Scholar databases. The manual search included journals and abstracts of international conferences, including oral podium presentations and oral poster presentations. The following keywords were used when searching for the relevant articles: "genitourinary syndrome", "vulvovaginal atrophy", "atrophic vaginitis", "postmenopausal symptoms", "laser therapy" and "fractional laser treatment". The evidence was reviewed for study design and methodology including selection and number of participants and clinical outcomes assessed. The subjective outcomes specific to the study objectives included follow-up time, subjective cure rates using questionnaires, success rates and complication rates. Data were extracted from the included studies and assessed for validity independently by two reviewers. One of the reviewers then entered the data into an Excel database. A third reviewer then checked the collated data quality. Study validity was formally assessed using the PRISMA checklist for this review [4]. A consensus approach was used to resolve differences between the reviewers.

CO_2 laser

MonaLisa Touch, which was developed in Europe by DEKA (Florence, Italy) and is now distributed in the United States by Cynosure, Inc. (Westford, MA), is a CO_2 laser designed to stimulate and promote the regeneration of collagen fibers and to restore hydration and elasticity within the vaginal mucosa. The MonaLisa fractional CO_2 laser uses patented Dermal Optical Thermolysis (DOT) therapy to apply laser energy to the vaginal walls in a noncontinuous mode in small 200-μm dots, thus directly affecting only a small percentage of the vaginal tissue. Different types of probes (360°, single-mirror, disposable, and vulvar applicator) accompany the device to allow adaptation to the specific clinical and/or anatomic needs of individual patients.

Er:YAG laser

The second type of laser used for the treatment of GSM is the Er:YAG laser with a wavelength of 2,940 nm, which emits laser energy in the mid-infrared region. This laser has 10 to 15 times the affinity for water absorption than the CO_2 laser at a wavelength of 10,600 nm. This treatment approach enables a deeper secondary thermal effect and controlled heating of the target mucous membrane of the vaginal wall.

Technique of the procedure

The technique for the procedure is the same for both types of laser. After inserting a specifically designed vaginal speculum, the probe is inserted into the speculum, with no direct contact with the vaginal mucosa. Thus, circular irradiation of the vaginal wall is performed, with four pulses given every 5 mm, retracting the probe by 5 mm each time (using the graduated scale on the probe). The procedure is repeated until the entrance of the vaginal canal is reached. This procedure is repeated three times, rotating the speculum by 45° each time. Finally, after removing the speculum and using a different probe, the vestibule and introitus are irradiated with a spot size of 7 mm, a fluence of 10 J/cm, with SMOOTH mode at 1.6 Hz.

Typically for both the CO_2 laser and the Er:YAG laser, an episode consists of three, short, procedures of 5–10 min at intervals of 4–6 weeks. Most patients report almost no discomfort other than a warming sensation, but if a patient prefers, a topical anesthetic cream can be applied prior to treatment. Some participants show improvement after one treatment procedure while some show improvement after two or three completed procedures. The treatment is an outpatient officebased procedure and no anesthesia or pain medication is required. Most women report some slight redness and or swelling and "some discomfort" that disappears within 1 or 2 days. No downtime is required, and regular activities can be resumed the same day. Intercourse can be resumed within a week after the procedure.

Results

The search identified 165 articles that met the inclusion criteria for at least one of the three objectives. Of the 165 articles identified, none was a randomized controlled trials (RCT). As a result, we included three case series without a control group and one case–control study that met our inclusion criteria and the subjective outcomes comparing laser therapy with hormonal treatment for the symptoms of GSM. Three case series without a control group [3, 5, 6] and one case–control study [7] were published as a full article and one case–control study was a conference abstract. As the conference abstract lacked quality and the design was unclear, it was excluded from the analysis. Table 1 shows the results of the search for "Genitourinary syndrome of menopause, Vulvovaginal atrophy AND Laser therapy". The total number of women included in the four studies was 220. Due to the lack of level 1 evidence (RCTs) and because the subjective cure rates were assessed using different types of questionnaires, it was not possible to compare the studies. For the purposes of this review, subjective cure rate or overall cure rates following laser therapy for GSM were calculated.

Table 1 Results of search for "Genitourinary syndrome of menopause, Vulvovaginal atrophy AND Laser therapy" (search undertaken on 1 March 2016)

Type of study	Term used	Number of articles
All articles	(No filter)	165
Randomized controlled trial	"Random allocation" (MeSH)	0
Cohort	"Cohort studies" (MeSH)	3
Case–control	"Case–control studies" (MeSH)	1
Case report	Case reports (publication type)	0

The studies reviewed used questionnaires to determine subjective cure rates including visual analog scales. The Er laser was used in only one study [8], and the CO_2 laser was used in the other three studies. In this analysis, all recruited patients experienced significant improvement in the different domains of the questionnaires used. The median follow-up time was 12 weeks. Table 2 shows the methodologies used for assessment.No adverse events were reported in any of the studies. No procedure needed to be stopped because of patient pain or intolerance.

Discussion

Review of collated evidence from the studies (level of evidence IV) to date suggests that laser therapy is effective in the treatment of GSM. The lack of RCTs made it difficult to undertake a meta-analysis based on the PRISMA statement [9]. In turn, this made it difficult to give weight to the selected studies. The Er laser was used in one of the four studies [8] and the CO_2 laser in the others [3, 5, 7]. In all the studies except the Er laser study [6] the patients were followed up for a maximum of 3 months. Therefore, assumptions cannot yet be made regarding the applicability or long-term effects of this treatment, either positive or negative. Lasers have become a very expensive option for the treatment of symptomatic GSM, without a single trial comparing active laser treatment to placebo. There is insufficient evidence on the longterm effects including safety. In all the published trials reviewed [3, 5–8, 10], 224 women have been studied and except in the study by Gambacciani et al. [6], the patients were followed up for only 12 weeks. Four of the studies [3, 6–8] showed improvement in the total Female Sexual Function Index (FSFI) score and the scores in each specific domain at 12 weeks to 6 months were compared with those at baseline. Most studies showed only "minimal" risk, and the procedures were performed on an outpatient or day-surgery basis. The main difference between the two lasers is that the CO_2 laser is ablative and the Er:YAG laser is nonablative. The cost of the treatment is not Medicare-rebatable or publically funded, hence the whole cost of Australian $1,000–1,500 per visit is paid by the patient.

It is important to highlight that the criteria for device clearance are much less stringent than criteria for drug approval, the clearance for the use of lasers in gynecology is not limited to or specifically indicated for the treatment of GSM, and unlike approval for new drugs, device clearance does not require large, double-blind, randomized, placebo-controlled trials to establish efficacy and safety endpoints.

In the 12-week pilot study by Salvatore et al. [3] symptoms were analyzed before and after three applications of fractional CO_2 laser, and the study showed a clear and significant improvement in symptoms. Salvatore et al. conducted a follow-up pilot study [3] in 50 postmenopausal women with symptoms suggestive of GSM who were dissatisfied with previous local estrogen therapies or who were nonresponders [3]. A key finding was that three laser applications improved the most bothersome GSM symptom in this 12week follow-up study. The study used a visual analog scale as well as the Vaginal Health Index Score (VHIS) to assess elasticity, pH, fluid volume, epithelial integrity, and moisture. However, changes in pH and percentage of superficial and parabasal

Table 2 Methodologies used for assessment in the four selected studies

Reference	Level of evidence	Outcome assessment	Outcome measures	Laser	No. of patients	Significance of symptom improvement (*p* value)
[6]	IV	Questionnaires (6 months)	VAS, VHIS, ICIQ-UI-SF	VEL	45	<0.01
[3]	IV	Questionnaires (12 weeks)	VAS, VHIS, SF-12	CO_2	50	<0.001
[7]	IV	Questionnaires (12 weeks)	FSFI, SF-12	CO_2	77	<0.001
[5]	IV	Questionnaires (30 days)	VHIS, VAS	CO_2	48	<0.0001

VEL vaginal erbium laser, *VAS* visual analog scale, *VHIS* Vaginal Health Index Score, *ICIQ-SF* International Consultation on Incontinence Questionnaire – short form

SF-12 Sexual Function 12, *FSFI* Female Sexual Function Index

cellular layers (vaginal maturation index) are not specifically mentioned. The study limitations include a small sample size, short duration, no long-term follow-up of patients and lack of active comparator groups. After use of the CO_2 microablative laser, the same group showed improvement in sexual function in women with vaginal atrophy [7]. Other groups have found similar results [6, 8].

Salvatore et al. [11] analyzed ten vaginal specimens from five women who underwent CO_2 fractional laser treatment while Zerbinati et al. [12] used light and electron microscopic evaluation to demonstrate remodeling of vaginal connective tissue without damage to surrounding tissues.

In the study by Salvatore et al. [7], 77 women with GSM were assessed for sexual function and quality of life after fractional microablative CO_2 laser treatment using the FSFI and the Short Form12 patient survey. In this study participants were assessed at baseline and at 12 weeks. A 10mm visual analog scale was used to measure overall satisfaction with sexual life and the intensity of vulvovaginal atrophy (VVA) symptoms (such as vaginal burning, vaginal itching, vaginal dryness, dyspareunia, and dysuria) before and after the study period. Of 20 women, 17 (85%) who were not sexually active because of severe VVA at baseline had regained a normal sexual life at the 12-week follow-up. There were some serious limitations of this small study including absence of a control arm with a sham laser procedure (given the high placebo response reported in interventional trials on female sexual dysfunction) or with hormone treatment. The open-label design of this study precluded effective control of potential serious confounding factors (e.g. higher motivation for coitus) and selection bias (women who were distressed and more motivated to improve in their sexual lives). In addition, the authors reported that the short follow-up precluded a comprehensive evaluation of the duration of laser treatment effects.

In the study by Gambacciani et al. [6], 45 postmenopausal women with GSM received three treatments at 30-day intervals with the Er:YAG laser, and the results were compared with the effects of a standard treatment of hormonal vaginal gel therapy in a group of 25 postmenopausal women. Compared with the vaginal gel, the Er:YAG laser treatment led to a significant decrease in both vaginal dryness and dyspareunia as well as a significant improvement in urinary incontinence. The effects were rapid and long lasting (up to the 24th week of the observation period), and the treatments were well tolerated with less than 3% of women discontinuing treatment due to adverse events. This may suggest that the effects of Er:YAG laser treatment are independent of any pretreatment, suggesting that the Er:YAG laser may be proposed for the treatment of postmenopausal women who cannot be treated with hormones (for example, breast cancer survivors).

An important limitation of these short-term studies is that the potential risks of long-term complications, such as scarring, were not addressed. In all the studies reviewed, patients were not monitored for concurrent use of intravaginal products or systemic medications that could have affected vaginal and vulvar health.

Although this FDA cleared laser technology is being marketed extensively to healthcare practitioners and directly to consumers, there is an urgent need for large, long-term, randomized, placebo-controlled and drugcontrolled studies to further evaluate the safety and efficacy of this procedure. It is important to understand that FDA clearance of a new medical device and its clinical indications requires a modest clinical study, in contrast to the high bar required for a comparable hormone medication and its clinical indications. The same technology may have been used in plastic surgery on facial tissues, but the potential for adverse effects when used on vulvovaginal tissues needs to be further studied and elucidated, perhaps in a postapproval registry. A multicenter study (VELAS) [8] using the Er laser is planned, but this study will have no control groups and is more of a registry-based study. Studies comparing this new expensive procedure with the gold standard treatment involving low-dose local hormones, moisturizers and the new selective estrogen receptor modulator (SERM) treatment are also warranted.

There are no contraindications to vaginal laser therapy except for its high cost. The evidence reviewed shows that laser therapy can be used for the treatment of GSM symptoms and does not show any adverse effects. However, there does not appear to be sufficient evidence of its long-term efficacy and other effects. The availability of robust, high-quality of evidence from RCTs will enable laser treatment to be compared with placebo or hormonal treatment. Similarly, well-designed case–control studies are required to further investigate the potential benefits, harm and efficacy of laser therapy in the treatment of GSM symptoms.

Although laser technology may hold promise for the future of GSM treatment, further long-term efficacy and safety data should be collected before fully embracing this expensive new technology.

Compliance with ethical standards

Conflicts of interest None.

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