



Rationale and design for fractional microablative CO₂ laser versus photothermal non-ablative erbium:YAG laser for the management of genitourinary syndrome of menopause: a non-inferiority, single-blind randomized controlled trial

R. Flint, L. Cardozo, T. Grigoriadis, A. Rantell, E. Pitsouni & S. Athanasiou

To cite this article: R. Flint, L. Cardozo, T. Grigoriadis, A. Rantell, E. Pitsouni & S. Athanasiou (2019): Rationale and design for fractional microablative CO₂ laser versus photothermal non-ablative erbium:YAG laser for the management of genitourinary syndrome of menopause: a non-inferiority, single-blind randomized controlled trial, *Climacteric*, DOI: [10.1080/13697137.2018.1559806](https://doi.org/10.1080/13697137.2018.1559806)

To link to this article: <https://doi.org/10.1080/13697137.2018.1559806>



Published online: 24 Jan 2019.



Submit your article to this journal [↗](#)



Article views: 6




View Crossmark data [↗](#)

ORIGINAL ARTICLE



Rationale and design for fractional microablative CO₂ laser versus photothermal non-ablative erbium:YAG laser for the management of genitourinary syndrome of menopause: a non-inferiority, single-blind randomized controlled trial

R. Flint^a, L. Cardozo^a, T. Grigoriadis^b , A. Rantell^a, E. Pitsouni^c and S. Athanasiou^c 

^aKing's College Hospital, London, UK; ^bFirst Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, 'Alexandra' Hospital, Athens, Greece; ^cFirst Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Athens, Greece

ABSTRACT

Genitourinary syndrome of menopause (GSM) is a common condition affecting up to 50% of postmenopausal women and up to 70% of postmenopausal breast cancer survivors. GSM is a chronic condition with a significant impact on sexual health and quality of life. The mainstay of treatment has been with symptomatic relief using topical emollients or lubricants. Second-line treatment is with topical vaginal estrogens to restore the physiology of the vaginal epithelium. For some, the latter is not suitable or acceptable. Newer treatments with ospemifene and vaginal lasers have now been introduced. The two main types of laser currently used for the treatment of GSM are the fractional microablative CO₂ laser and the non-ablative photothermal erbium:YAG laser.

We present a study protocol for a multicenter, prospective, non-inferiority, single-blinded, randomized controlled trial comparing the fractional microablative CO₂ laser versus the photothermal non-ablative erbium:YAG laser for the management of GSM.

We will recruit 88 postmenopausal women across two sites who will be randomized to one of the two laser groups. Participants will all have GSM symptoms and a Vaginal Health Index Score < 15. All participants will receive an active treatment. Each participant will receive three applications of vaginal laser 1 month apart and will be followed up at 1 month, 6 months, and 12 months. Our primary outcomes will look at all changes of GSM symptoms (dryness, dyspareunia, itching, burning, dysuria, frequency, urgency), urinary incontinence (if present), and overall sexual satisfaction. Both subjective and objective means will be used to assess participants.

The findings of this trial have the potential to allow clinicians and women suffering from GSM to make an informed decision when opting for a specific laser type. The trial will add to the current growing body of evidence for the safe use of vaginal lasers in GSM as an alternative treatment. We hope this trial will provide robust and long-term data for the safe use of both lasers.

ARTICLE HISTORY

Received 3 November 2018
Revised 23 November 2018
Accepted 6 December 2018
Published online 23 January 2019

KEYWORDS

Laser; genitourinary syndrome of menopause; vulvovaginal atrophy; erbium:YAG laser; CO₂ laser

Introduction

Genitourinary syndrome of menopause (GSM) is the new terminology for 'vulvovaginal atrophy (VVA)'¹. The GSM definition was introduced to describe more accurately the urogenital changes and the local symptoms occurring after the menopause in comparison to the terms of VVA vaginitis¹. Hence, it involves clinical symptoms and signs from both the genital tract and the lower urinary tract (LUTS)¹. Although women may present with some or all of the clinical symptoms and signs¹, the most common symptom of VVA/GSM is vaginal dryness²⁻⁴. Vaginal dryness occurs at or soon after the menopause, with a subsequent increase in prevalence as the postmenopausal years progress³, and is associated with an increase of LUTS⁵. GSM is chronic in nature and may worsen over time, jeopardizing sexual function and quality of life in up to 50% of postmenopausal women⁶⁻¹⁰. In breast cancer survivors, GSM can affect up to 70% of the postmenopausal patients when compared to postmenopausal women without breast cancer^{11,12}.

The therapeutic management of GSM includes lubricants and moisturizers as first-line therapy, and low-dose vaginal estrogens as the second line, especially for women with a history of estrogen-dependent cancer^{7,13}. However, moisturizers, which can be used at anytime, and lubricants, which can only be used for symptomatic relief during sexual intercourse, have limited efficacy. They do not restore the local physiology and they are ineffective when LUTS are present. Hence, vaginal estrogens remain the only local therapeutic option for the restoration of local physiology and management of VVA symptoms and LUTS. However, the quality of evidence is low or very low when estrogen efficacy is compared to placebo¹⁴. In addition, evidence from the European REal Women's Views of Treatment Options for Menopausal Vaginal ChangEs (REVIVE) Survey suggests that women are concerned about the long-term use and safety of vaginal estrogens⁴. Furthermore, they can be reluctant or unwilling to use them due to the possibility of developing cancer.

Recently, intravaginal laser therapy has been proposed for the management of GSM. Two laser technologies – micro-ablative fractional CO₂ laser (CO₂ laser) (SmartXide² V²LR, Monalisa Touch; DEKA, Florence, Italy) and non-ablative photothermal Erbium:YAG laser (Er:YAG laser) (Fotona SmoothTM XS; Fotona, Ljubljana, Slovenia) – have been used in women with GSM^{9–22}. These two lasers differ in wavelength, water absorption, and tissue penetration. The CO₂ laser has a wavelength of 10,600 nm that allows a superficial microablative effect in soft tissues and a pulsed beam that protects the tissues from possible overheating damage. The laser beam is produced in a fractional manner, creating small spots (called DOTs) alternating in the parts of tissue treated. Moreover, a D-pulse mode consists of two parts: a constant, high-energy peak power, for rapid superficial removal of the atrophic epithelium with low water content; and a lower peak power with longer emission times that allows the energy heat to penetrate deeper into the epithelium. This D-pulse mode combined with DOTs treats with specificity, with a low percentage of the vaginal wall achieving regeneration and protection of the surrounding tissues. The power (range 0.5–60 W), dwell time (range 100–1000 μs), and spacing (range 100–1000 μm) that define the quantity of energy, depth (SmartStak parameter, from 1 to 3), and D-pulse are applicable to be selected from the machine software. The Er:YAG laser has a wavelength of 2940 nm and a non-ablative deep thermal effect on the vaginal epithelium, using a pulse-controlled pattern. It uses a SMOOTHTM mode that has low fluence and long-shaped erbium pulses that allow a controlled deep thermal effect, without ablation. The diameter of the laser beam (spot size) is 7 mm, at a frequency of 1.6 Hz and a fluence of 5.5 J/cm² or 10 J/cm² depending on the RenovalaseTM phase. These are default values that can be changed with the use of the respective computer software.

All available studies consistently suggest that both lasers (CO₂ laser and Er:YAG laser) are safe and have a high efficacy for alleviation of vaginal dryness and dyspareunia, as well as restoring the local physiology^{15–28}.

Direct comparison between laser and topical vaginal estrogens has been undertaken by Gambacciani and Levancini¹⁸ and Gaspar et al.¹⁹. Both studies showed a statistically significant reduction in all GSM symptoms when looking at the CO₂ laser. In one study the relief of symptoms was more prominent in the laser group, which remained statistically significant for longer¹⁹.

A recent systematic review and meta-analysis of 14 observational studies by Pitsouni et al.²⁹, looking at both laser types, found that all GSM symptoms and urinary incontinence (UI) decreased significantly and consistently in all publications. They also found a significant improvement in the Female Sexual Function Index questionnaire score and overall sexual satisfaction, which has also been seen in other publications^{25,29}. It is important to note that a lot of these studies were not sham or placebo controlled.

Currently, there is a lack of robust studies comparing the two laser technologies for the management of postmenopausal women with GSM. The aim of the current study is to assess whether the CO₂ laser results in non-inferior

alleviation of GSM symptoms compared to the Er:YAG laser. Specifically, we will compare subjective and objective measurements of symptoms and clinical signs of GSM between groups of postmenopausal women with GSM receiving treatment with the CO₂ laser or Er:YAG laser.

Methods

Design

This study will be conducted at two centers (King's College, London, UK and Alexandra Hospital, Athens, Greece) according to the Helsinki Declaration. It will be a single-blind, randomized parallel-group, allocation-concealed, non-inferiority trial. Two groups of postmenopausal women with symptoms and clinical signs of GSM will be enrolled. The efficacy and safety of the intravaginal CO₂ laser (SmartXide² V²LR, Monalisa Touch; DEKA) will be compared to the intravaginal Er:YAG laser (Fotona SmoothTM XS; Fotona). Approval from the Ethics Committees of both hospitals has been granted and the study has been registered on ClinicalTrials.gov (NCT03288883).

Inclusion criteria

Recruited participants will meet the following criteria at the time of randomization:

- (1) Dryness and dyspareunia with moderate to severe intensity.
- (2) Vaginal Health Index Score (VHIS) ≤ 15.
- (3) Absence of menstruation for at least 12 months.
- (4) Recent negative cervical smear test (for women over 65 years old, a negative smear test on leaving screening).

Exclusion criteria

Participants will be excluded under the following circumstances:

- (1) Not willing to abstain from vaginal intercourse for 1 week following the laser therapy.
- (2) Use of hormonal therapy within 6 months prior to study inclusion (systemic or local, this includes estrogens, progestogens, and corticosteroids).
- (3) Acute urinary tract infections.
- (4) Pre-existing diagnosis of overactive bladder not controlled on treatment or treatment started less than 1 month previously.
- (5) Any treatment with botulinum toxin A for overactive bladder within the last 6 months.
- (6) History of a genital fistula, a thin rectovaginal septum as determined by the investigator, or history of a fourth-degree laceration during screening physical examination (e.g. perineal body).
- (7) Active sexually transmitted disease upon vaginal examination (as determined by the investigator) that precludes treatment or any other vaginal infection.
- (8) Active or history of genital herpes.

- (9) Prolapse stages > II (according to the Pelvic Organs Prolapse Quantification system).
- (10) History of radiotherapy for cervical or uterine cancer.
- (11) Medical condition that may interfere with participants' compliance to the protocol.
- (12) Any history of breast cancer estrogen receptor positive receiving current treatments with selective estrogen receptor modulator or aromatase inhibitor.

Withdrawal management

Participants with one of the following criteria will be allowed or may be required to withdraw from the study:

- (1) non-compliance to the study protocol; or
- (2) major or unexpected or uncontrolled adverse events related to the laser therapy

Protocol

Description of the intervention

Group A

Three CO₂ laser therapies will be applied at monthly intervals. The laser parameters will be as follows:

- (1) Power: 30 W.
- (2) Dwell time: 1000 μ s.
- (3) Spacing: 1000 μ m.
- (4) Depth: SmartStak parameter from 1 to 3 depending on the treatment status.
- (5) D-pulse mode.
- (6) At the introitus the power will be reduced to 24 W.

Group B

Three Er:YAG laser therapies will be applied at monthly intervals. The treatment protocol will be following the standard parameters from the manufacturer:

- (1) Phase I Renovalase™ mode with (a) fluence of 1.75 J/cm², (b) SMOOTH™ mode frequency 1.6 Hz, and (c) spot size 7 mm.
- (2) Phase II Renovalase™ mode with (a) fluence 10 J/cm², (b) SMOOTH™ mode frequency 1.6 Hz, and (c) spot size 7 mm.

Primary outcomes

The primary outcomes will be regarded as all changes in GSM symptoms (dryness, dyspareunia, itching, burning, dysuria, frequency, urgency), UI (if present), and overall sexual satisfaction. In order to assess the primary outcomes, the participants will be asked to complete the following questionnaires/outcome measures:

- (1) A 3-day voiding diary.

- (2) A 10-cm Visual Analog Scale (0–10) for the intensity of each GSM symptom (dryness, dyspareunia, itching, burning, dysuria, frequency, urgency, and overall), UI, and overall sexual satisfaction. The left extreme of the scale will indicate 'absence of pain' and the right extreme 'as bad as could be'. Regarding sexual satisfaction, the left extreme of the scale will indicate 'no sexual satisfaction' and the right extreme 'as good as could be'.
- (3) Frequency of sexual intercourse (times per month).
- (4) Female Sexual Function Index³⁰.

Secondary outcomes

The secondary outcomes will be the following measurements:

- (1) Day-to-Day Impact of Vaginal Aging Questionnaire³¹.
- (2) King's Health Questionnaire.
- (3) Patients Global Impression of Improvement.
- (4) pH of the vaginal fluid: pH indicator strips will be applied against the lateral vaginal wall using sterile forceps and will be read by both evaluators independently.
- (5) The VHIS will be evaluated by both evaluators. A form including the five VHIS components (elasticity, epithelial integrity, pH, moisture, and fluid volume) will be completed by each evaluator independently. (Each component could receive scores from 1 to 5, where 1 is the worst and 5 the best value. $VHIS \leq 15$ defines atrophy.)
- (6) Vaginal Maturation Value (VMV): a vaginal smear will be obtained from the lateral vaginal wall using a spatula and will be stained according to the Papanicolaou technique. The Vaginal Maturation Index is evaluated by defining the percentage of superficial, intermediate, and parabasal epithelial cells on the smear. The VMV is calculated using the formula: $VMV = [(1 \times \%superficial) + (0.5 \times \%intermediate) + (0 \times \%parabasal)]$.

Numbers

A sample size of 40 patients per group will establish a non-inferiority trial at a power of 80% and a level of significance of 0.05. Considering an expected average drop-out rate of 10%, 44 participants will be required per group and 88 participants in total³².

Randomization

Randomization will be performed 1:1 by an independent statistician using the free web page of sealed envelope (<https://www.sealedenvelope.com/simple-randomiser/v1/lists>). In order to guarantee the group balance at each site, the block randomization kit will be used. Allocation concealment will be performed by sealed opaque envelopes. The first half will be sent to the Urogynaecology Unit of King's College Hospital, London, UK and the second half to the Urogynaecology Unit of Alexandra Hospital, Athens, Greece. The sealed opaque envelopes will be retained in a safe locked place and only an independent nurse will have access.

Follow-up

Participants will be followed up at 1 month, 6 months, and 12 months post last laser treatment. An adverse events diary will be kept by all participants, which will be reviewed before every laser treatment. At each follow-up visit, patients will fill in the previously described questionnaires and comparisons from baseline to follow-up will be made. Participants will act as their own controls because comparison to baseline will be sufficient to compare changes.

Throughout the trial, participants will be questioned regarding adverse events and required to fill an adverse events diary which will allow us to monitor any adverse events noted either as a consequence of the laser or incidental findings.

Discussion

Vaginal lasers have been shown to restore the vagina's physiology and effectively treat GSM²⁹. There are data to show that vaginal lasers are as efficacious as topical vaginal estrogens and have a longer duration of action, suggesting that this is a promising new treatment.

There has been a growing number of cohort studies published in this area supporting their use for GSM. There are, however, currently few randomized controlled trials with long-term follow-up. Following the release of a US Food and Drug Administration warning in July 2018 regarding the use of vaginal lasers, more vigilance and robust data are required to substantiate the claim that they are a safe and an effective treatment for GSM. We hope that the outcomes of this study and the logging of adverse events will add to the knowledge and safety data for the lasers.

In the present paper, we present the protocol for a large multicenter study on the evaluation of the efficacy of the CO₂ laser vs. the Er:YAG laser for the treatment of GSM. To our knowledge, this is the first randomized, single-blind protocol investigating both laser types.

The outcome of this study will provide much-needed robust long-term data to allow patients and clinicians alike to make an informed decision over the use of vaginal lasers for GSM.

Conflict of interest The authors report no conflict of interest.

Source of funding Nil.

ORCID

T. Grigoriadis  <http://orcid.org/0000-0002-4301-8775>

S. Athanasiou  <http://orcid.org/0000-0003-0005-0369>

References

- Portman DJ, Gass ML. On behalf of the Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Climacteric*. 2014;17:557–63
- Wysocki S, Kingsberg S, Krychman M. Management of vaginal atrophy: Implications from the REVIVE survey. *Clin Med Insights Reprod Health* 2014;8:23–30
- Nappi RE, Particco M, Biglia N, et al. Attitudes and perceptions towards vulvar and vaginal atrophy in Italian post-menopausal women: Evidence from the European REVIVE survey. *Maturitas*. 2016;91:74–80
- Nappi RE, Palacios S, Panay N, et al. Vulvar and vaginal atrophy in four European countries: Evidence from the European REVIVE survey. *Climacteric* 2016;19:188–97
- Juliato CR, Baccaro LF, Pedro AO, et al. Factors associated with urinary incontinence in middle-aged women: a population-based household survey. *Int Urogynecol J* 2017;28:423–9
- Sturdee DW, Panay N. Recommendations for the management of postmenopausal vaginal atrophy. *Climacteric* 2010;13:509–22
- Management of symptomatic vulvovaginal atrophy: 2013 position statement of the North American Menopause Society. *Menopause* 2013;20:888–902
- Ettinger B, Hait H, Reape KZ, et al. Measuring symptom relief in studies of vaginal and vulvar atrophy: the most bothersome symptom approach. *Menopause* 2008;15:885–9
- Parish SJ, Nappi RE, Rychman ML, et al. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. *Int J Womens Health* 2013;5:437–47
- Oge T, Hassa H, Aydin Y, et al. The relationship between urogenital symptoms and climacteric complaints. *Climacteric* 2013;16:646–52
- Lester J, Pahouja G, Andersen B, et al. Atrophic vaginitis in breast cancer survivors: a difficult survivorship issue. *J Pers Med* 2015;5:50–66
- Crandall C, Petersen L, Ganz PA, et al. Association of breast cancer and its therapy with menopause-related symptoms. *Menopause* 2004;11:519–30
- ACOG Committee Opinion No. 659. The use of vaginal estrogen in women with a history of Estrogen-dependent breast cancer. *Obstet Gynecol* 2016;127:e93–6
- Rahn DD, Carberry C, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol* 2014;124:1147–56
- Athanasiou S, Pitsouni E, Antonopoulou S, et al. The effect of microablative fractional CO₂ laser on vaginal flora of postmenopausal women. *Climacteric* 2016;19:512–18
- Gambacciani M, Levancini M, Cervigni M. Vaginal erbium laser: the second-generation thermotherapy for the genitourinary syndrome of menopause. *Climacteric* 2015;18:757–63
- Gambacciani M, Levancini M. Short-term effect of vaginal erbium laser on the genitourinary syndrome of menopause. *Minerva Ginecol* 2015;67:97–102
- Gambacciani M, Levancini M. Vaginal erbium laser: the second generation thermotherapy for the Genitourinary Syndrome of Menopause (GSM) in breast cancer survivors. A preliminary report of a pilot study. *Int J Gynecol Obstet* 2015;27:9–11
- Gaspar A, Brandi H, Gomez V, et al. Efficacy of Erbium:YAG laser treatment compared to topical estriol treatment for symptoms of genitourinary syndrome of menopause. *Laser Surg Med* 2017;49:160–8
- Perino A, Calligaro A, Forlani F, et al. Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO₂ laser. *Maturitas* 2015;80:296–301
- Perino A, Cucinella G, Gugliotta G, et al. Is vaginal fractional CO₂ laser treatment effective in improving overactive bladder symptoms in post-menopausal patients? Preliminary results. *Eur Rev Med Pharmacol* 2016;20:2491–7
- Pieralli A, Fallani MG, Becorpi A, et al. Fractional CO₂ laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. *Arch Gynecol Oncol* 2016;294:841–6
- Pitsouni E, Grigoriadis T, Tsiveleka A, Microablative fractional CO₂-laser and the genitourinary syndrome of menopause: an observational study. *Maturitas* 2016;94:131–6

24. Salvatore S, Maggiore ULB, Origoni M, et al. Microablative fractional CO2 laser improves dyspareunia related to vulvovaginal atrophy: a pilot study. *J Endom Pelv Pain Disord*. 2014; doi: [10.5301/je.5000184](https://doi.org/10.5301/je.5000184)
25. Salvatore S, Nappi RE, Parma M, et al. Sexual function after fractional microablative CO2 laser in women with vulvovaginal atrophy. *Climacteric* 2015;18:219–25
26. Salvatore S, Nappi RE, Zerbinati N, et al. A 12-week treatment with fractional CO2 laser for vulvovaginal atrophy: a pilot study. *Climacteric* 2014;17:363–9
27. Sokol E, Karram M. An assessment of the safety and efficacy of a fractional CO2 laser system for the treatment of vulvovaginal atrophy. *Menopause* 2016;23:1102–7
28. Zerbinati N, Serati M, Origoni M, et al. Microscopic and ultrastructural modifications of postmenopausal atrophic dioxide treatment. *Laser Med Sci*. 2015;30:429–36.
29. Pitsouni E, Grigoriadis T, Falagas ME, et al. Laser therapy for genitourinary syndrome of menopause. A systematic review and meta-analysis. *Maturitas* 2017;103:78–88
30. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000;26:191–208
31. Huang AJ, Gregorich SE, Kuppermann M, et al. The Day-to-Day impact of vaginal aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and Well-being in postmenopausal women. *Menopause* 2015;22:144–54
32. Zhong B. How to calculate sample size in randomized controlled trial? *J Thorac Dis* 2009;1:51–4
33. Weber MA, Limpens J, Roovers JPWR. Assessment of vaginal atrophy: a review. *Int Urogynecol J* 2015;26:15–28