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CLINICAL TRIAL

Vaginal CO_2 laser for the treatment of vulvovaginal atrophy in women with breast cancer: LAAVA pilot study

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Abstract

Purpose Vulvovaginal atrophy (VVA) is a commonly reported issue among breast cancer patients, and its aetiology is multifactorial. Treatment is difficult in these women, particularly because the use of oestrogens has traditionally been discouraged. Vaginal laser treatment has been reported to improve symptoms. We aimed to assess the impact on symptoms and sexual function of vaginal laser in women with early breast cancer (EBC).

Methods We performed a single-arm investigator initiated pilot study of female EBC patients with symptomatic VVA. A total of 3 vaginal laser treatments were administered 4 weeks apart. Questionnaires were completed at baseline, 4, 8 and 12 weeks. Our primary endpoint was symptomatic improvement of VVA at 12 weeks on 10 cm visual analogue scales. Our secondary endpoints were improvement in sexual function using the Female Sexual Function Index (FSFI) and patient-reported improvements in symptoms, sexual function and quality of life. Statistical analysis was performed with a Wilcoxon Signed Rank test.

Results 26 patients were enrolled between February 2016 and August 2017. All patients were post-menopausal, 25 of whom had received anti-oestrogen therapy for their breast cancer. Questionnaire compliance was high (98%) and all patients received the three pre-planned treatments. There was significant improvement in each of the VVA symptoms: dryness ($p < 0.001$), itch ($p < 0.001$), burning ($p = 0.003$), dysuria ($p < 0.001$) and dyspareunia ($p < 0.001$). Patients also reported improvement in sexual function on the FSFI ($p \leq 0.001$).

Conclusions Patients receiving vaginal laser had improvement in VVA symptoms and sexual function. Further randomised sham-controlled trials are needed to further assess this treatment.

Keywords Early breast cancer · Vulvovaginal atrophy · Genitourinary symptoms of menopause · Vaginal laser · Fractional CO_2 laser

Abbreviations

EBC	Early breast cancer
FSFI	Female Sexual Function Index
GSM	Genitourinary symptoms of menopause
HRT	Hormone replacement therapy
MCID	Minimum clinically important difference
QOL	Quality of life
SD	Standard deviation
VAS	Visual analogue scale
VHI	Vaginal Health Index
VVA	Vulvovaginal atrophy

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Introduction

Vulvovaginal atrophy (VVA) or genitourinary symptoms of menopause (GSM) is commonly reported in breast cancer survivors [1], with an increased prevalence of symptoms compared to their age-matched peers [2, 3]. VVA is caused by chronic oestrogen depletion and in breast cancer patients, there are multiple factors that contribute to its development including chemotherapy, premature onset of menopause and systemic endocrine therapy. VVA involves a constellation of symptoms including vaginal dryness, vaginal itch or burning, dysuria, urinary urgency, urinary incontinence, dyspareunia, loss of libido and dysfunction of arousal and orgasm [4, 5]. However, unlike other menopausal symptoms, VVA symptoms tend to persist and even worsen over time [6]. Chronic oestrogen depletion leads to both physiological and structural changes in the genital tissues, with subsequent decrease in blood flow and secretions, thinning of the epithelium, loss of elasticity and increased pH [4]. These atrophic changes lead to the vaginal, urinary and sexual symptoms of VVA and can have a negative impact on patients' quality of life (QOL) and sexual function [7].

Women with breast cancer who require chemotherapy or hormonal treatment such as GnRH analogues, tamoxifen and aromatase inhibitors frequently experience VVA. This is particularly a problem in young women who experience premature menopause as a result of their breast cancer treatment. Endocrine therapy can either cause VVA or worsen pre-existing VVA, although aromatase inhibitors are more likely to cause VVA symptoms than tamoxifen [4, 8].

In the women who have symptomatic VVA, there are numerous therapies available for treatment including smoking cessation, vaginal moisturisers and lubricants, oral hormone replacement therapy (HRT) and local oestrogen therapies [6]. However, there is concern that both oral and topical oestrogens may increase the risk of cancer recurrence in women with hormone receptor-positive breast cancer, so many oncologists and patients avoid their use [4]. Effective treatment options for VVA in this population are therefore limited.

Fractional CO_2 laser technology has been demonstrated to induce connective tissue remodelling in the vaginal wall with minimal adverse effects [9]. In the initial single-arm prospective pilot study performed by Salvatore et al. postmenopausal women received between one and three treatments, delivered approximately 4 weeks apart [10]. This study demonstrated improvements in VVA symptoms, QOL and sexual function [7, 10]. The first randomised double-blinded sham-controlled trial in vaginal laser, published by Cruz et al. in 2018, compared three treatment arms: vaginal laser + placebo oestriol cream (L), vaginal laser and oestriol cream (LE) and sham laser + oestriol cream (E) in post-menopausal women with symptoms of VVA [11]. 45 patients were recruited (15 in each arm) with all three arms showing an improvement in the Vaginal Health Index (VHI) at 20 weeks. The arms which included laser (L, LE) showed improvement in dryness, burning and dyspareunia, with the oestriol arm (E) showing improvement only in dryness. There was an improvement in sexual function using the Female Sexual Function Index (FSFI) in the laser and oestriol group (LE) only. Cruz et al.'s study suggested that laser plus oestriol cream (LE) patients derived more benefit than those receiving sham laser and oestriol cream (E) but they did not compare laser alone to sham laser alone, and area that needs further exploration. This study is important as it is the first sham-controlled trial assessing the benefit of vaginal laser in women with VVA. However, the study is very small and only powered to detect a small difference in VHI score.

The efficacy of vaginal laser treatment in breast cancer survivors has been reported in two studies. A retrospective study of 82 patients with a history of breast cancer performed by Pagano et al. showed improvement in dyspareunia and urinary symptoms with laser therapy [12]. A prospective study performed by Pieralli involving 50 breast cancer patients showed a benefit of vaginal laser in improving dyspareunia and clinician assessment of VVA using the VHI [13]. However, both studies did not assess other symptoms of VVA or sexual function. There is still limited evidence as to the benefit of this costly treatment in breast cancer survivors and no sham-controlled trials have been reported in the breast cancer population.

Methods

Participants

Between February 2016 and August 2017, women aged > 18 years with a history of stage I–III breast cancer who have symptomatic VVA (at least one of vaginal dryness, itch, burning, dysuria and dyspareunia) were recruited. Patients must have received endocrine therapy (aromatase inhibitor or selective estrogen receptor modulator), had an oophorectomy or be post-menopausal at the time of enrolment. Patients who had used local or systemic oestrogen therapies in the preceding 6 months, topical moisturisers or lubricants in the preceding 30 days or those with any medical contraindication to vaginal laser treatment were excluded. The study was approved by the Human Research Ethics Committee at the Sydney Adventist Hospital.

Baseline data collection

At baseline, participants completed questionnaires on demographics, clinical characteristics and risk factors for VVA. Vulvovaginal atrophy symptoms were assessed using a 10 cm visual analogue scale (VAS) for each of the 5 VVA symptoms: vaginal dryness, itch, burning, dysuria and dyspareunia. The VAS scale uses 0–10 scale to rate symptoms from no symptoms (0) to worst possible symptoms (10). The FSFI was used to evaluate sexual function. This is a validated tool in women with sexual dysfunction disorders and cancer survivors and is comprised of 19 questions covering 6 domains (sexual desire, arousal, lubrication, orgasm, satisfaction and pain) with a minimum total score of 4 and a maximum total score of 95. QOL was assessed using the SF-12 questionnaire, a validated tool with 12 questions covering 8 domains (physical functioning, role-physical, pain, general health, vitality, social functioning, role-emotional and mental health). We assessed patient-reported improvement in symptoms, QOL and sexual function using 5-item Likert scales (5 possible answers when asked if they thought they had improvement in these areas: strongly disagree, disagree, neutral, agree, strongly agree).

Vaginal laser protocol

Fractional microablative CO_2 laser was delivered with the SmartXide2 system (Monalisa Touch) system. A vaginal laser probe was inserted and 360° treatment of the vaginal mucosa was delivered via manual rotation. Treatments were given 3×, 4 weeks apart. The laser was set to a power of 40 W, dwell time of 1000 µs and spacing of 1000 µm with a smart stack of 2.0. The treatment was administered by an experienced, trained gynaecologist.

Follow-up data collection

Follow-up questionnaires were collected prior to each treatment and 4 weeks after completion of the final treatment (4, 8, 12 weeks post baseline).

Study endpoints and statistical calculation

Evaluable subjects were defined as those who signed consent and completed at least one laser treatment. The primary endpoint was the difference in VVA symptoms at 12 weeks on a 10 cm VAS scale. Our secondary endpoints were difference in FSFI and its domains, sexual function, QOL and patient-reported improvement at 12 weeks.

Statistical analysis was performed using 'IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). Wilcoxon Signed Rank test was used to determine statistical significance, with a two-tailed $p \leq 0.05$ considered significant.

Results

Accrual, eligibility and evaluability

Between February 2016 and August 2017 at total number of 29 patients were screened and 26 were treated. A CONSORT diagram is shown in Fig. 1.

Participant characteristics

The median age of participants was 56 years. All patients were post-menopausal and most patients (96%) had received prior endocrine therapy. The median time since breast cancer diagnosis was 3.26 years (0.58–11.36).

Baseline patient characteristics are listed in Table 1.

Treatment and questionnaire adherence

All patients received the 3 pre-planned vaginal laser treatments.

Questionnaire compliance was high for symptom and sexual function scoring (98%). However, the QOL questionnaire compliance was lower (88.5%) largely due to administration error.

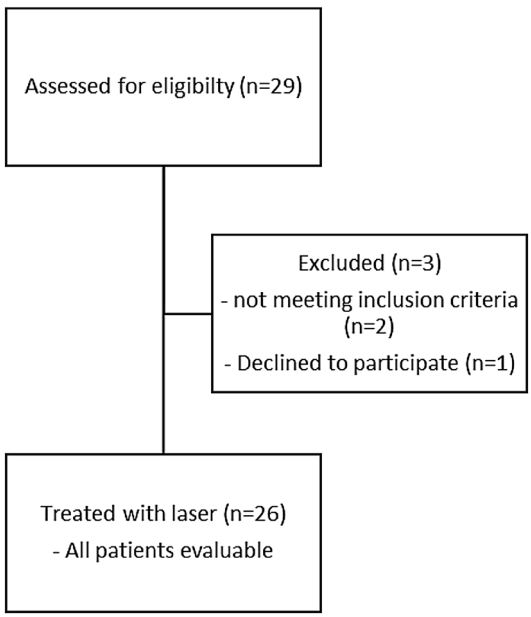

Fig. 1 Consort diagram of LAAVA pilot study

Table 1 Participant characteristics

Characteristic	Number	Percentage
Age (median)	55	
Menopause		
Yes	26	100
No	0	
Previous local oestrogens		
Yes	11	42
No	15	58
Previous systemic HRT		
Yes	7	27
No	19	73
Prior endocrine therapy for EBC		
Tamoxifen	12	48
Letrozole/anastrozole	10	40
Exemestane	1	4
Goserelin + anastrozole	1	4
None	1	4

HRT hormone replacement therapy, *EBC* early breast cancer

Vulvovaginal symptoms and sexual function

At 12 weeks, there was a significant improvement in all VVA symptoms: vaginal dryness ($p < 0.001$), itch ($p < 0.001$), burning ($p = 0.003$), dysuria ($p < 0.001$) and dyspareunia ($p < 0.001$). Mean values at each timepoint and the mean absolute change at 12 weeks are listed in Table 2.

At baseline 13/26 (50%) patients were sexually active and by 12 weeks 18/26 (69%) patients reported being sexually active with a partner. Sexual function on FSFI was improved at 12 weeks ($p < 0.001$), including patients who were not sexually active with a partner. The improvement in FSFI at 12 weeks was found across all 6 domains: desire ($p = 0.036$), arousal ($p = 0.001$), lubrication ($p = 0.001$), orgasm ($p = 0.001$), satisfaction ($p = 0.009$) and pain ($p = 0.002$) (Table 3).

Patient-reported improvement

Likert scales were used to assess patient-reported improvements in symptoms overall, sexual function overall and QOL. 73% of patients felt their symptoms had improved with laser treatment. Patients reported an improvement in sexual function overall in 50% of patients (with further 30% of patients reporting neutral feelings) and in QOL in 65% of patients.

Discussion

In this pilot study of vaginal laser treatment for breast cancer survivors with symptoms of vaginal atrophy, we observed an improvement in all 5 cardinal symptoms of VVA using VAS scores. Patients also reported an improvement in sexual function on the FSFI as a whole, as well as in each of the 6 domains of the FSFI. Symptoms and sexual function are important to patients [1] and given that symptoms usually worsen over time [6] a safe and effective intervention is needed.

There have been several studies suggesting that vaginal laser treatment can benefit post-menopausal women, including a recent small double-blinded sham-controlled trial [11]. More recently, there has been a retrospective report and a prospective study [12, 13] looking at this treatment in breast cancer survivors which have suggested a benefit in dyspareunia, urinary symptoms and clinical assessment of VVA. Unfortunately, these studies did not assess other symptoms of VVA which also may be bothersome to women, including vaginal dryness. Although Pieralli et al. and Pagano et al. used different endpoints in their study, our study showed similarly positive results for patients receiving this treatment, which warrants further research.

The major strengths of our study were the high (100%)-treatment rate in our enrolled group, relatively high

Table 2 Mean score and change in symptoms on a 10 cm visual analogue scale

	Mean score ± SD	Mean absolute change at 12 weeks	*P* value*
Dryness			
Baseline	8.31 (±1.05)	5.10	< 0.001
4 weeks	5.76 (±2.28)		
8 weeks	3.92 (±2.00)		
12 weeks	3.21 (±2.15)		
Itch			
Baseline	3.42 (±2.80)	2.76	< 0.001
4 weeks	2.2 (±2.47)		
8 weeks	1.42 (±1.82)		
12 weeks	0.67 (±1.05)		
Burning			
Baseline	4.31 (±3.40)	2.85	0.003
4 weeks	3.12 (±2.88)		
8 weeks	2.04 (±2.07)		
12 weeks	1.46 (±2.34)		
Dysuria			
Baseline	2.65 (±2.48)	2.11	< 0.001
4 weeks	1.92 (±2.32)		
8 weeks	1.38 (±2.14)		
12 weeks	0.54 (±0.98)		
Dyspareunia			
Baseline	8.83 (±2.65)	4.31	< 0.001
4 weeks	6.23 (±2.33)		
8 weeks	4.83 (±2.13)		
12 weeks	4.53 (±3.11)		

Visual analogue scale (0–10, where 0 = no symptom and 10 = severe symptom)

SD standard deviation

**p* values apply to baseline versus 12-week assessment

Table 3 Change in mean score of FSFI and its domains at 12 weeks

FSFI domains	Mean score ± SD	*P* value
Desire		
Baseline	2.38 (± 1.14)	< 0.036
12 weeks	2.87 (± 1.23)	
Arousal		
Baseline	1.92 (± 1.38))	0.001
12 weeks	3.33 (± 1.56)	
Lubrication		
Baseline	1.45 (± 1.18)	0.001
12 weeks	3.08 (± 1.76)	
Orgasm		
Baseline	1.89 (± 1.84)	0.001
12 weeks	3.27 (± 1.99)	
Satisfaction		
Baseline	2.23 (± 1.63)	0.009
12 weeks	3.43 (± 1.63)	
Pain		
Baseline	1.17 (± 1.35)	0.002
12 weeks	2.81 (± 1.90)	
Total score		
Baseline	11.08 (± 6.97)	< 0.001
12 weeks	18.77 (± 8.76)	

patient adherence with questionnaires and the selection of a specific population of early breast cancer survivors with risk factors for significant VVA. We also used validated self-reported outcome measures for VVA symptoms and sexual function. The main limitation of our study is the single-arm design of the trial, with no control group. Therefore, we cannot exclude placebo as a potential cause of the improved symptoms. However, this trial did demonstrate feasibility of performing further studies in this area in our breast cancer patients.

Symptoms of VVA on VAS scores was used as the primary mode of assessing response to treatment in this study. However, there has not been a well-established minimal clinically important difference (MCID) for VVA symptoms. The FSFI score for sexual function similarly has no standard accepted MCID. There was also no objective clinical assessment in this study (e.g. VHI, Maturation Index or pH) and we therefore rely on patient-reported outcomes only for assessment of improvements with the laser treatment. We felt that patient-reported outcomes were more clinically relevant, but ideally both would be used for assessment of patients in studies.

This pilot study has demonstrated promising improvements in symptoms and sexual function, and this may offer a good option for breast cancer survivors with long-term treatment-related genitourinary sequelae. However, there have to date been no sham-controlled trials of vaginal laser in women with breast cancer. Sham-controlled trials, as well as those comparing laser to other potential topical treatments in breast cancer patients are needed to further our knowledge in this area. We are currently recruiting to a randomised double-blinded sham-controlled vaginal laser trial for women with a history of early breast cancer at two centres comparing sham-laser to active laser treatment (Clinicaltrial.gov ID: NCT03628092).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Research involving human participants and/or animals This study was approved by the Adventist HealthCare Limited Human Research Ethics Committee (HREC). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

References

1. Mazzarello S, Hutton B, Ibrahim MFK, Jacobs C, Shorr R, Smith S, Ng T, Clemons M (2015) Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials. Breast Cancer Res Treat 152(1):1–8. https://doi.org/10.1007/s10549-015-3434-z
2. Lester J, Bernhard L, Ryan-Wenger N (2012) A self-report instrument that describes urogenital atrophy symptoms in breast cancer survivors. West J Nurs Res 34(1):72–96. https://doi.org/10.1177/0193945910391483
3. Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N (1999) Risk of menopause during the 1st year after breast cancer diagnosis. J Clin Oncol 17(8):2365–2370. https://doi.org/10.1200/jco.1999.17.8.2365
4. Lester J, Pahouja G, Andersen B, Lustberg M (2015) Atrophic vaginitis in breast cancer survivors: a difficult survivorship issue. J Pers Med 5(2):50–66. https://doi.org/10.3390/jpm5020050
5. Portman DJ, Gass ML (2014) 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. Menopause 21(10):1063–1068. https://doi.org/10.1097/gme.0000000000000329
6. Biglia N, Bounous VE, Sgro LG, D'Alonzo M, Pecchio S, Nappi RE (2015) Genitourinary syndrome of menopause in breast cancer survivors: are we facing new and safe hopes? Clinical Breast Cancer 15(6):413–420. https://doi.org/10.1016/j.clbc.2015.06.005
7. Salvatore S, Nappi RE, Parma M, Chionna R, Lagona F, Zerbinati N, Ferrero S, Origoni M, Candiani M, Leone Roberti Maggiore U (2015) Sexual function after fractional microablative CO(2) laser in women with vulvovaginal atrophy. Climacteric 18(2):219–225. https://doi.org/10.3109/13697137.2014.975197

8. Fallowfield L, Cella D, Cuzick J, Francis S, Locker G, Howell A (2004) Quality of life of postmenopausal women in the arimidex, tamoxifen, alone or in combination (ATAC) adjuvant breast cancer trial. J Clin Oncol 22(21):4261–4271. https://doi.org/10.1200/jco.2004.08.029
9. Zerbinati N, Serati M, Origoni M, Candiani M, Iannitti T, Salvatore S, Marotta F, Calligaro A (2015) Microscopic and ultrastructural modifications of postmenopausal atrophic vaginal mucosa after fractional carbon dioxide laser treatment. Lasers Med Sci 30(1):429–436. https://doi.org/10.1007/s10103-014-1677-2
10. Salvatore S, Nappi RE, Zerbinati N, Calligaro A, Ferrero S, Origoni M, Candiani M, Leone Roberti Maggiore U (2014) A 12-week treatment with fractional CO_2 laser for vulvovaginal atrophy: a pilot study. Climacteric 17(4):363–369. https://doi.org/10.3109/13697137.2014.899347
11. Cruz VL, Steiner ML, Pompei LM, Strufaldi R, Fonseca FLA, Santiago LHS, Wajsfeld T, Fernandes CE (2018) Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO_2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. Menopause 25(1):21–28. https://doi.org/10.1097/gme.0000000000000955
12. Pagano T, De Rosa P, Vallone R, Schettini F, Arpino G, Giuliano M, Lauria R, De Santo I, Conforti A, Gallo A, Nazzaro G, De Placido S, Locci M, De Placido G (2018) Fractional microablative CO_2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study. Menopause 25(6):657–662. https://doi.org/10.1097/gme.0000000000001053
13. Pieralli A, Fallani MG, Becorpi A, Bianchi C, Corioni S, Longinotti M, Tredici Z, Guaschino S (2016) Fractional CO_2 laser for vulvovaginal atrophy (VVA) dyspareunia relief in breast cancer survivors. Arch Gynecol Obstet 294(4):841–846. https://doi.org/10.1007/s00404-016-4118-6