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Research article

Treatment of Vaginal Atrophy Using Fractional Microablative CO_2 Laser in Post-Menopausal Women with Breast Cancer on Aromatase Inhibitors: A Pilot Study

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Abstract

Aim: Fractional CO_2 intra-vaginal laser is a non-hormone-based therapy designed to treat vaginal atrophy (VA). The feasibility of CO_2 laser in post-menopausal women with breast cancer (BC) on aromatase inhibitors (AI) was evaluated.Method Stage I-III post-menopausal BC patients on an AI with symptomatic VA received 3 CO_2 laser treatments scheduled 4 weeks apart. Clinical assessment, vaginal cytology, biopsy and patient questionnaires were undertaken at baseline and 12-week post treatment. The primary endpoint was improvement in the Urogenital Atrophy Questionnaire (UAQ) and the Vaginal Health Index Score (VHIS). Secondary end points included improvement in sexual function on Female Sexual Function Index (FSFI) and change in vaginal epithelial cytology and histology. Results Between May 2017 and July 2020, 33 patients were enrolled. 27 patients completed all 3 pre-planned treatments and post-treatment assessment (T1 n=30; T2 n=30; T3 n=28); post-Rx n=27). Patient-reported vaginal dryness (100 vs 48%, p=<0.001), irritation/itch (56 vs 19%, p=0.008), pain (63 vs 11%, p=0.001) and dyspareunia (89 vs 78%, p=0.371) reduced at 12-weeks post treatment. VHIS increased by a mean 4.1-points at final assessment (p=<0.001). Patient reported vaginal dryness improved on UAQ (p=<0.001). No clinically meaningful improvement in sexual function domains were detected on UAQ and FSFI questionnaires. Conclusions CO_2 laser is a feasible non-hormonal option for post-menopausal BC patients on AI therapy resulting in improvements in patient-reported vaginal dryness and clinician-assessed VA. This intervention is less effective for treating sexual function symptoms that may be associated with VA.

Key words: Vaginal atrophy, genitourinary syndrome, laser,menopause, breast cancer

Introduction

Genitourinary Syndrome of Menopause (GSM) is caused by the reduction of circulating oestrogen resulting in vaginal atrophy, epithelial inflammation and changes to vaginal pH and flora [1,2]. Symptoms of GSM include vaginal dryness, dyspareunia and urinary symptoms of urgency, dysuria and recurrent urinary tract infections [3].

GSM is a source of major distress and morbidity in the breast cancer population. Between 50 to 75% of patients with breast cancer report symptoms of GSM [4]. In post-menopausal wom-

en with hormone-receptor positive breast cancer, symptoms of GSM may be further exacerbated by the use of aromatase inhibitors (AI) due to profound suppression of oestrogen in all tissues [5]. Therapeutic options for GSM are typically limited to topical lubricants or oestrogens and hormone replacement therapy in this population. For these women, the use of hormone-based therapies is often not an acceptable option unless symptoms of GSM are severe or refractory due to concerns regarding increased recurrence risk [6,7].

Fractional microablative CO_2 (MonaLisa Touch™) laser is a non-surgical, non-hormone based therapy effective in early phase studies for treatment of GSM. Fractional CO_2 laser aims to improve microcirculation below the level of the vaginal mucosa resulting in formation of new collagen on atrophic tissue [8,9]. Studies evaluating the use of three sessions of fractional CO_2 laser (MonaLisa Touch®) in a general population of post-menopausal women resulted in a significant improvement in vulvovaginal atrophy and sexual function 12 weeks post treatment without any major adverse events [8,10] with clinical benefit sustained at 12 months after the last laser treatment [11]. Conversely, a more recent randomised study comparing CO_2 laser to sham treatment showed no significant improvement in vaginal symptoms at 12 months. Over 50% of participants in this study had a history of previously treated breast cancer [12].

In women with hormone-positive breast cancer experiencing GSM whilst on adjuvant AI therapy, there is a clear need to explore non-hormone-based options with potential longer-term efficacy. This study evaluates the feasibility of fractional CO_2 laser (MonaLisa Touch®) specifically in post-menopausal women with hormone-positive breast cancer and its impact on symptoms of GSM evaluated by clinical examination, patient questionnaires and tissue analysis of the vaginal epithelium.

Materials and Methods

Patients

Post-menopausal women aged ≥18 years with Stage I-III hormone-positive breast cancer on an aromatase inhibitor for a minimum of 6 months reporting GSM symptoms defined by one of more of the following: vaginal dryness, vaginal irritation or itch, vaginal discomfort or dyspareunia were eligible for enrolment. Exclusion criteria included concurrent use of hormone replacement therapy or topical oestrogens and evidence of lichen sclerosis or infection on clinical examination.

Study design and treatment

Fractional CO_2 laser was delivered using the MonaLisa Touch® system. Patients received 3 treatment sessions scheduled 4 weeks apart using the 22mm diameter vaginal laser probe applied to the vaginal mucosa. Probe specifications were set to validated parameters: 30 watts with a dwell time of 1000µs, dot spacing of 1000µm and smart stack parameter from 1.0-3.0. All treatments were administered by one specialist gynaecologist trained in the CO_2 MonaLisa Touch® technique.

Trial assessments

Clinician assessment, vaginal cytology, vaginal epithelial punch biopsy and patient questionnaires were undertaken at baseline and 12-weeks post treatment. Clinician assessment included a gynaecological examination and record of the Vaginal Health Index Score (VHIS). Patient questionnaires completed at baseline and 12-weeks post-treatment included the Urogenital Atrophy Questionnaire (UAQ) and Female Sexual Function Index (FSFI) [13,14].

End points

The primary end point was severity of GSM symptoms at 12 weeks post completion of laser therapy measured by the clinician-assessed Vaginal Health Index Score (VHIS) and patient-assessed Urogenital Atrophy Questionnaire (UAQ) score. The Vaginal Health Index Score (VHIS) [Appendix A] is a clinician assessment tool that evaluates the appearance of vaginal mucosa (elasticity, paleness, vaginal discharge, mucosal integrity, moisture) and vaginal pH. Each factor is scored on a scale of 1 to 5 and then summed to provide the VHI score. A score of less than 14 indicates vaginal atrophy. The Urogenital Atrophy Questionnaire (UAQ) is a standardised, validated self-reported 15-item questionnaire designed to identify and evaluate severity of symptoms secondary to GSM.

Secondary end points were cytological change in vaginal atrophy measured by the Vaginal Epithelial Maturation Index (VEMI), histological change in vaginal atrophy assessed by central pathology review and sexual function assessed by the Female Sexual Function Index (FSFI) score at 12 weeks post completion of laser therapy.

The Vaginal Epithelial Maturation Index (VEMI) is a ratio of the three cell types (parabasal, intermediate and superficial cell type) of the vaginal epithelium obtained by cytological sampling of the vaginal mucosa and examined using the Papanicolou stain. Vaginal atrophy is indicated by the predominance of parabasal cells due to the absence of oestrogenic stimulation on the vaginal epithelium [15,16]. Improvement in the VEMI is measured by an increase in ratio of superficial to parabasal cells on vaginal smear cytology collected at baseline and 12 weeks post completion of laser treatment. Histology was performed on 4mm vaginal mucosal punch biopsies at baseline and 12 weeks post-treatment and examined using routine (haematoxylin and eosin) and Periodic-acid Schiff (PAS) stains. Epithelial thickness was measured in micrometres taken between the epithelial rete, in well-oriented mucosa without squash artefact.

The Female Sexual Function Index (FSFI) is a standardised, validated self-reported 19-item questionnaire designed to assess domains of sexual functioning in clinical trials. The FSFI assesses sexual function in six domains including desire, arousal, lubrication, orgasm, satisfaction and pain, with a score <26.55 indicating female sexual dysfunction.

Statistical analysis

Evaluable patients were defined as those who completed three laser treatments all baseline and 12-week end-of-treatment assessments. Analyses were conducted using R 4.2 (https://cran.r-project.org/). Data was expressed using mean (SD) and median (Percentile 25-Percentile75) or (min-Max) for numeric normal and non-normal variables, respectively, and frequency (percent) for categorical variables. Comparison of baseline and end-of-treatment measurements, paired t-, Wilcoxon signed rank, sign and McNemar tests were undertaken where appro-

priate. The correlation among change in scores were assessed using Pearson correlation coefficients. The normality of data was decided on descriptive measures of distribution, skewness and kurtosis (within ±1.5, and ±2, respectively). P-values <0.05 were considered significant.

Trial Oversight

The trial protocol and all amendments were approved by the Cabrini Health Ethics Committee, Melbourne, Australia. The trial was conducted in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans (© Commonwealth of Australia 2007), the NHMRC Australian Code for the Responsible Conduct of Research (© Australian Government 2007) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. All patients provided written informed consent prior to enrolment.

Results

Patients

Between May 2017 and July 2020, 33 patients were enrolled. The study closed early due to slow recruitment and COVID-19 restrictions. Baseline characteristics are listed in Table 1. The median age was 52 years (range 32-76). A history of oophorectomy (n=15, 45%), prior chemotherapy (n=24, 73%) and bilateral mastectomy (n=9, 27%) were reported. Twenty-seven patients completed all 3 pre-planned laser treatments and post-treatment assessment (T1 n=30; T2 n=30; T3 n=28); post-Rx n=27) and eligible for final analysis. Reasons for study withdrawal (n=5) include cessation of AI (n=1), second malignancy (n=1), pain post biopsy (n=1) and unknown (n=2).

Primary end point

Patient-reported outcomes

Pre and post treatment evaluations: patient-reported vaginal dryness (100 vs 48%, p=<0.001), irritation/itch (56 vs 19%, p=0.008), pain (63 vs 11%, p=0.001) all significantly reduced in incidence at 12 weeks post completion of CO_2 laser treatment (Table 2). No significant reduction in patient reported dyspareunia (89 vs 78%, p=0.371) was observed. At the 12-week post-treatment assessment, a significant increase of 52% (CI 33.6-69.7%, n=14/27, p=<0.001) of the study population reported improvement in the frequency of vaginal dryness; defined as experiencing vaginal dryness 'none' or 'some' of the time as opposed to 'most' or 'all' of the time on UAQ (Item 8, Figure 1). Significant reduction in the frequency of genitourinary symptoms such as dysuria, nocturia and vaginal odour was also observed (UAQ Item 1, 5 and 9) (all p=<0.05). No clinically meaningful improvement in most items relating to sexual function (UAQ Item 11-15) was detected on UAQ.

Clinician-assessed outcomes

The median Vaginal Health Index Score (VHIS) improved from 9.3 at baseline vs 13.4 at 12-weeks post treatment with a score ≤14 indicating vaginal atrophy. Median VHIS by domain at baseline vs 12-weeks post treatment was: elasticity (2/5 vs 3/5), fluid volume (2/5 vs 3/5), pH (1/5 vs 1/5), epithelial integrity (2/5 vs 4/5) and moisture (2/5 vs 3/5). The majority of evaluable patients (n=25/27) demonstrated improvement in VHIS score at 12-weeks post treatment. VHIS improved by a mean of 4.1-points at final assessment (p=<0.001), attributed to a

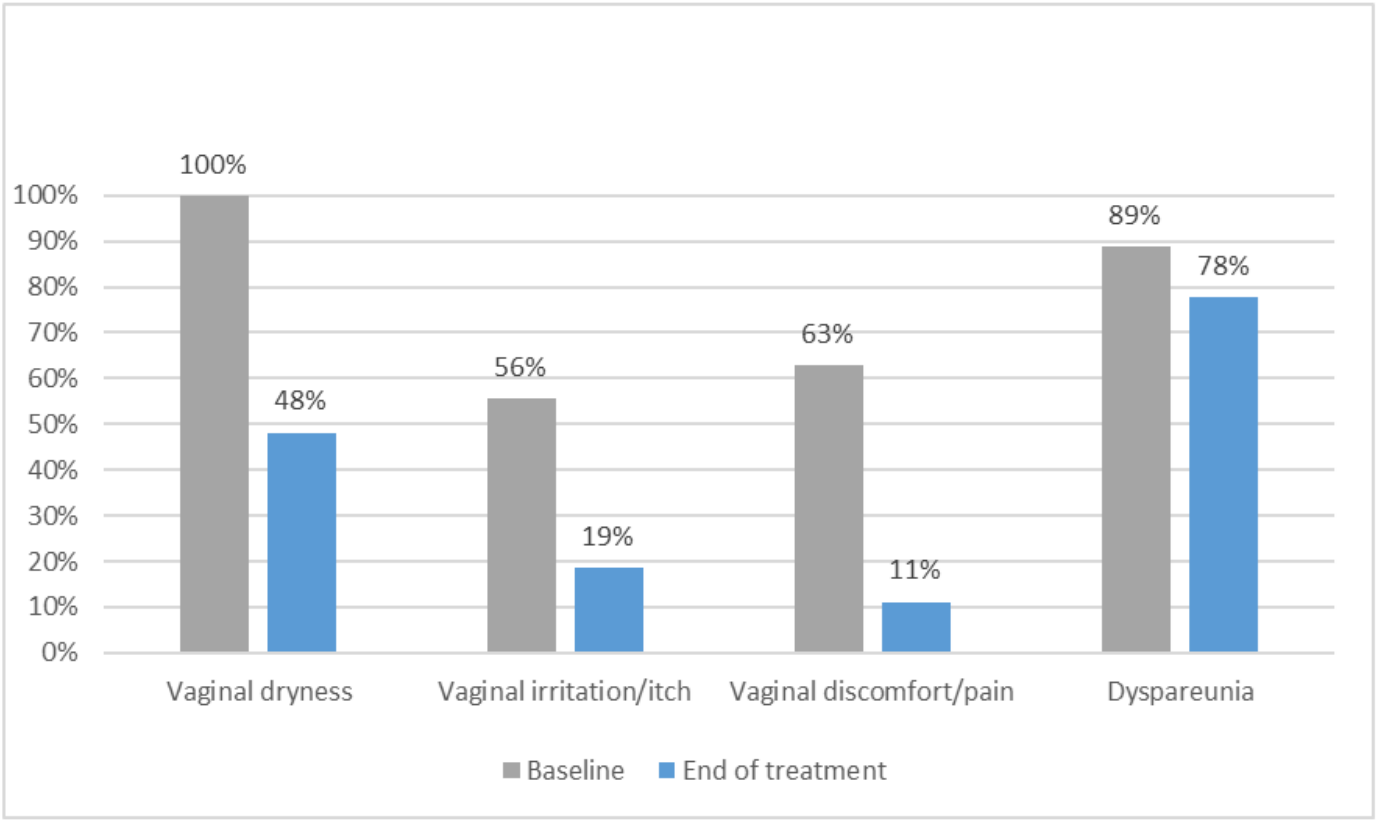

Figure 1. Baseline vs end of treatment patient reported Genitourinary Symptoms of Menopause (GSM)

Table 1. Patient demographics

	n=33 (%)
Age median (range)	52 (32-76)
Stage	
I	6 (18%)
II	16 (48%)
III	9 (27%)
Not reported	2 (6%)
Aromatase inhibitor	
Anastrozole	13 (39%)
Letrozole	13 (39%)
Exemestane	7 (21%)
Prior oophorectomy	15 (45%)
Prior chemotherapy	24 (73%)
Surgery type	
Wide local excision	7 (21%)
Mastectomy	13 (39%)
Bilateral mastectomy	9 (27%)
Not reported	4 (12%)
Treatment course completed	
Treatment 1	30 (82%)
Treatment 2	30 (82%)
Treatment 3	28 (85%)

significant improvement in epithelial integrity (p=<0.001), moisture (p=<0.001), fluid volume (p=<0.001) score and elasticity (p=0.006) scores (Appendix B).

Secondary end-points

Sexual function

FSFI score improved at 12-weeks post-treatment with median FSFI score increasing from 10.5/36 at baseline to 15.5/36 (p=0.04). An improvement in median score across most FSFI domains were observed (Table 3), however the 12-week end-of-treatment score remained <26.55, the threshold indicative of ongoing female sexual dysfunction.

Cytology

Baseline and 12-week post treatment cytological assessment and calculation of the VEMI ratio was undertaken for each patient. No significant increase was found in the ratio of superficial to parabasal cells at 12-weeks post treatment to indicate cytological change consistent with reduction in vaginal atrophy. The median percentage of parabasal cells at baseline vs 12-week post treatment was 87% (range 1-97%) vs 84% (range 6-98%) respectively. The median percentage of superficial cells at 12-weeks post treatment remained unchanged at 0% compared to baseline.

Histology

Increase in epithelial thickness (median 0.1mm, range -0.06-0.14mm) was observed in n=15 (56%) of 12-week post treatment

Table 2. Baseline vs end of treatment Urogenital Atrophy Questionnaire (UAQ) scores

	None/some of the time (n=27)		Most/all of the time (n=27)		P-value [SGT]
	Baseline	EOT	Baseline	EOT	
Item 1: When I urinate, I feel a burning sensation in the opening where urine comes out	26	27	1	0	**0.008**
Item 2: When I have the urge or urinate, I cannot wait and must hurry to the toilet	23	25	4	2	0.424
Item 3: I leak urine when I cough, sneeze or laugh	23	26	4	1	0.065
Item 4: When I am done urinating, I do not feel like my bladder is empty	25	26	1	1	0.754
Item 5: I have to get up during the night to urinate	13	16	14	11	**<0.001**
Item 6: I feel irritation or discomfort on the skin of my external genitals as I wipe with toilet tissue	24	27	3	0	0.070
Item 7: My vagina itches	24	27	3	0	0.070
Item 8: My vagina feels dry	5	19	21	8	**<0.001**
Item 9: I notice an unpleasant odour from my vagina	24	26	3	1	**0.031**
Item 10: I have a white or creamy discharge from my vagina	27	27	0	0	0.219
Item 11: The thought of sexual activity worries me because it might cause pain in my genital area	5	12	22	15	**<0.001**
Item 12: I am able to talk with my partners about my sexual concerns	7	9	17	14	0.688
Item 13: I am interested in sexual activity	17	20	9	7	0.146
Item 14: I desire sexual activity	20	23	7	4	0.109
Item 15: I am happy with my sex life	22	24	4	3	0.774

EOT: 12-week end of treatment assessment

SGT: sign test

Table 3. Baseline vs end of treatment FSFI domains and total score

Sub-scales/scale	Baseline		End of treatment		P-value [W]
	Median (P25-P75)	Mean(SD)	Median (P25-P75)	Mean(SD)	
Desire	4.0 (2.0-5.0)	3.82 (1.69)	4.0 (4.0-6.0)	4.67 (1.57)	0.011
Arousal	7.0 (4.0-11.0)	6.82 (4.21)	9.0 (4.0-13.0)	8.59 (5.67)	0.091
Lubrication	4.0 (3.0-9.0)	5.33 (4.10)	7.0 (0.0-15.0)	7.93 (6.87)	0.079
Orgasm	4.0 (2.0-8.0)	5.04 (4.06)	5.0 (0.0-10.0)	5.93 (5.19)	0.346
Satisfaction	4.0 (3.0-7.0)	5.63 (3.86)	10.0 (2.0-12.0)	7.67 (5.20)	0.106
Pain	3.0 (0.0-5.0)	3.22 (3.34)	4.0 (0.0-10.0)	5.22 (4.77)	0.026
Total FSFI score	10.5 (6.0-17.3)	11.49 (6.71)	15.5 (3.9-24.4)	15.28 (9.28)	0.040

Med: Median; P: percentile
W: Wilcoxon signed rank test

Sub-scales/scale was constructed using sum over related items

biopsy specimens with associated increased spongiosis and intracytoplasmic glycogen on central pathology review. The degree of chronic inflammation of the vaginal mucosa did not appear to bear any relation to the epithelial thickness. Epithelial thickness remained unchanged in n=4 (15%) and reduced in n=8 (30%) biopsies at 12-weeks post treatment (range 0.02-0.06mm). No significant correlation was found between increase in epithelial thickness at 12-weeks post treatment and clinical improvement measured by VHI score (r=0.260; 95% CI -0.069-1.0; p=0.095) and FSFI score (r= -0.016; 95% CI: -1.0-0.31; p=0.469).

Discussion

In this single-arm study, fractional CO_2 laser was a feasible non-hormonal treatment for some symptoms of GSM in post-menopausal BC patients on an AI. Three courses of CO_2 laser therapy resulted in a reduction in patient-reported vaginal dryness, itch and pain at 12 weeks post treatment in addition to improvements in vaginal atrophy predominantly due to an increase in epithelial integrity score on clinical assessment.

While an improvement in physiological factors were improved, our study found fractional CO_2 laser was less effective in treating sexual function symptoms in women with treated breast cancer on AI therapy. Whilst total FSFI score increased post treatment, the score continued to reflect ongoing sexual dysfunction in this population. We also did not observe significant improvements in multiple sexual function domains including arousal, lubrication, orgasm or satisfaction when assessed in patient questionnaires.

In post-menopausal women with breast cancer on endocrine therapy, prior studies by Pearson, et al. [17] and Quick, et al. [18] have shown fractional CO_2 laser results in both improved patient-reported symptoms of vaginal atrophy and improvement in sexual function. Marked improvement in sexual function with laser therapy were not observed in our cohort. Sexual function, desire and sexual arousability are complex and, in this study population, can be severely impacted by their diagnosis of breast cancer and its treatment such as mastectomy and endocrine therapy [19]. Population based studies report significant reduction in feelings of sexual attractiveness and comfort during sexual intimacy at 2 years post mastectomy, including those women who had undergone breast reconstruction [20].

Notably, the impact of fractional CO_2 laser intervention may have been diminished in our cohort due to the prevalence of sexual dysfunction at enrolment indicated by baseline FSFI score in addition to high proportion of enrolled patients with a history of bilateral mastectomy (27%) and locally advanced disease. Our results indicate interventions that targeting vaginal atrophy and dryness alone are insufficient as sole treatment of GSM; particularly if sexual dysfunction symptoms are prominent. A holistic approach to GSM treatment may involve addressing psychological and body image factors together with sexuality in addition to interventions that target vaginal atrophy.

To date, this is the only study of women with breast cancer on AI therapy that has comprehensively evaluated the feasibility of fractional CO_2 laser utilising the triad of clinician assessment, patient-reported questionnaires and tissue analysis. Fractional CO_2 laser resulted in an increase in vaginal epithelial thickness in over half of evaluable patients, demonstrating objective evidence of treatment effect in women subject to the ongoing anti-oestrogenic effect of concurrent AI therapy. Interestingly, no correlation was found between the degree of epithelial thickness and clinical improvement measured by VHIS or FSFI. Results may be limited due to the small sample size and further work is needed to characterise laser-induced remodelling at the epithelial and sub-mucosal level in relation to clinical effect. Histological assessment of the submucosal tissues would require specialised staining techniques and is beyond the scope of this pilot study.

Limitations of this study are acknowledged. The small cohort, pilot design and early closure of recruitment limits any definitive conclusions being drawn. The study also was not designed to assess the duration of treatment effect or efficacy of laser treatment compared to other interventions such as lubricant or a placebo-controlled sham laser.

Whilst a 2019 meta-analysis including ten observational studies largely supports the use of fractional CO_2 laser in breast cancer survivors, this intervention has not been widely adopted for the treatment of GSM due to lack of randomised and long-term safety data [21]. This issue will be addressed in the SHE CAN study (NCT04606550) that will assess fractional CO_2 laser compared to topical vaginal oestrogen in women with breast cancer with GSM that will incorporate up to two years of follow up.

Conclusion

In conclusion, fractional CO_2 laser is a feasible non-hormonal

intervention resulting in improvement in patient-reported vaginal dryness and clinician-assessed vaginal atrophy in post-menopausal BC patients on AI therapy. The intervention was less effective for treating sexual function symptoms associated with GSM. Further work is required to explore and improve management of sexual dysfunction in this cohort.

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Conflicts of Interest

None

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