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Fractional microablative CO_2 laser in breast cancer survivors affected by iatrogenic vulvovaginal atrophy after failure of nonestrogenic local treatments: a retrospective study

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Abstract

Objective: Vulvovaginal atrophy (VVA) is a condition frequently observed in menopause. Its symptoms can significantly affect the quality of life of patients. Since VVA is related to estrogen deficiency, chemotherapy and hormone therapy for breast cancer (BC) might cause VVA by inducing menopause. Given the lack of effective treatment for VVA in BC survivors, we retrospectively evaluated the efficacy and tolerability of fractional microablative CO_2 laser therapy in these patients.

Methods: We treated 82 BC survivors with three cycles of CO_2 laser after failure of topical nonestrogenic therapy. The severity of symptoms was assessed with a visual analog scale (VAS) at baseline and after completion of laser therapy. Differences in mean VAS scores of each symptom before and after treatment were assessed with multiple *t* tests for pairwise comparisons. Multivariate analyses were used to adjust the final mean scores for the main confounding factors.

Results: Pre versus post-treatment differences in mean VAS scores were significant for sensitivity during sexual intercourse, vaginal dryness, itching/stinging, dyspareunia and dysuria ($P < 0.001$ for all), bleeding ($P = 0.001$), probe insertion ($P = 0.001$), and movement-related pain ($P = 0.011$). Multivariate analyses confirmed that results were significant, irrespective of patients' age and type of adjuvant therapy.

Conclusion: This study shows that CO_2 laser treatment is effective and safe in BC patients with iatrogenic menopause. However, the optimal number of cycles to administer and the need for retreatment remain to be defined. Prospective trials are needed to compare CO_2 laser therapy with therapeutic alternatives.

Key Words: Breast cancer – Chemotherapy – CO_2 laser – Hormone receptor – Hormone therapy – Menopause – Vaginal atrophy.

Vulvovaginal atrophy (VVA) affects 25% to 50% of women from 4 to 5 years after menopause,[1] and is associated with vaginal flatulence, dryness, leucorrhea, vaginal itching and/or stinging, vaginal bleeding, dysuria, dyspareunia, and/or reduced sensitivity during sexual intercourse. VVA is caused by menopausal estrogen deficiency—a condition that results in shortening and narrowing of the vagina, and a dry thick epithelium that is prone to inflammation and friability. Also, the collagen and elastin fiber structure of the vaginal mucosae undergo changes that result in reduced elasticity and a decrease in mucus secretion with a consequent loss of lubrication. Alterations in the vulvovaginal microenvironment also induce changes in the local bacterial flora that increase the risk of genitourinary infections.[2] Symptoms of VVA tend to worsen if not treated.[1]

Since VVA is related to estrogen deficiency, chemotherapy (CT) and hormone therapy (HT) for breast cancer (BC) might cause VVA by inducing menopause.[3,4] Notably, VVA can negatively affect the quality of life of BC survivors due to its bothersome symptoms, recurrent genitourinary infections, and negative impact on sexual function.[5-7] Moreover, VVA symptoms can occur sooner and be more severe in patients with CT or HT-induced menopause than in women with physiological menopause.[8] Unfortunately, VVA is underdiagnosed mainly

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All authors conceived the study. RV, PDR, and TP performed the laser technique and collected data. FS performed the statistical analyses. FS, PDR, RV, TP, ML, and GDP interpreted the data. FS, PDR, RV, and TP wrote the article. All authors revised and approved the final manuscript.

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TABLE 1. *Main treatments for vulvovaginal atrophy, and indications and current issues in breast cancer patients*

Pharmacological treatments	Indications and current issues in BC
Nonhormonal vaginal moisturizers and lubricants (water or silicon-based lubricants, ozonized creams, hyaluronic acid vaginal creams, topical liquid lidocaine)	First-line therapy in BCS, usually mild and temporary efficacy, might interfere with partner's erectile function
Systemic estrogens	Contraindicated in HR+ BC, concerns for other subtypes
Low-dose vaginal estrogens	Very effective but significant concerns in HR+ BC
Oral ospemiphene	Effective but no clinical trial results available in BC
Androgen therapy	Experimental; concerns about peripheral aromatization of androgens to estrogen
Nonpharmacological treatments	
Fractional microablative CO_2 laser	Promising efficacy and safety, but unknown best number of cycles, lack of long follow-up periods, lack of prospective validation in BCS
Vaginal dilators of graduated size	Need for larger trials
Pelvic floor physical therapy	Need for larger trials
Couple counsellng	—
Psychological interventions	—

BC, breast cancer; BCS, breast cancer survivors; HR+, hormone receptor-positive.

because patients are reluctant to discuss intimate and sexual issues with their physicians.[9,10]

Consequent to the decrease of BC mortality over the past decade,[11] CT and HT-induced VVA is an increasing challenge that must be addressed to improve the quality of life of patients.[12] Moreover, VVA can impact survival because up to 20% of BC survivors cease or consider stopping adjuvant HT because of menopausal symptoms including VVA.[13]

Unfortunately, there is no effective standard of care for VVA induced by iatrogenic menopause.[14] Table 1 shows the current and experimental therapeutic options available. The use of estrogen therapy may be contraindicated in women with BC, most likely in women with an ER-positive malignancy and who are being treated with an antiestrogen therapy. Low-dose local estrogens are also effective, but there are significant concerns about their use, at least in HR-positive BC, since a small study showed a slight increase in estrogen levels after 2 weeks of local estrogen formulations in women undergoing aromatase inhibitor adjuvant therapy.[15] A newer compound—the selective estrogen receptor modulator ospemiphene—was recently reported to have a promising safety and efficacy profile in physiological menopause in both observational and prospective clinical trials.[16-19] However, despite compelling preclinical evidence of safety and efficacy,[20-22] there is no general consensus regarding its use in women affected by BC undergoing CT and/or HT. Furthermore, a case of venous thromboembolism after ospemiphene treatment was reported in long-term safety studies.[23]

In December 2014, the Federal Drug Administration approved fractional microablative CO_2 laser therapy for vaginal itching and dryness, pain during sexual intercourse, and vaginal laxity. This technique was shown to be effective in the physiological postmenopausal setting.[24,25] In a histological study, fractional microablative CO_2 laser induced the production of new collagen and elastic fibers, thereby remodeling connective tissues without damaging adjacent tissues.[26] These histological effects translated into improved sexual function and higher overall satisfaction with sexual life.[24-28]

Although fractional microablative CO_2 laser is an effective treatment strategy for VVA induced by physiological menopause, only two small studies have evaluated its effects on VVA in menopause induced by systemic anti-BC treatment.[28,29] Iatrogenic menopausal symptoms are more frequent and more severe than those observed after natural menopause.[30,31] This difference might be related to the abrupt rather than progressive decrease in exposure of the vaginal mucosa to estrogen[30] and also to a shorter duration of this exposure in iatrogenic versus physiological menopause. Moreover, when ovarian function is suppressed in iatrogenic menopause, the ovarian production of testosterone ceases, whereas it is minimally preserved in physiological menopause,[32] and testosterone induces proliferation of the vaginal epithelium.[33] All these physio-pathological differences might affect the efficacy of VVA therapies, including laser therapy.

Given the efficacy of fractional microablative CO_2 laser treatment in physiologic menopause, we retrospectively evaluated its efficacy and tolerability in a large cohort of women affected by BC with CT or HT-induced VVA who did not respond to first-line vaginal nonestrogenic moisturizers and lubricants.

METHODS

Population characteristics and anticancer treatments

Eighty-two women affected by BC and VVA induced or worsened by adjuvant CT and/or HT were treated with fractional microablative CO_2 laser at the Reproductive Medicine Unit of the University of Naples Federico II between April 2015 and May 2017. The treatment was offered after failure of vaginal nonestrogenic moisturizers and lubricants, mostly ozonized creams and hyaluronic acid creams. All patients had undergone tumor surgery. Fifty-two patients (63%) were <50 years old, 30 (37%) were ≥ 50 years old, and the median age was 44 years. Ten of these women (12%) were postmenopausal before starting adjuvant CT or HT, and VVA, if present, was worsened by adjuvant anticancer therapies. Fifty-two patients (63%) received adjuvant or

neoadjuvant CT, 61 (74%) were treated with adjuvant HT, and 42 (51%) received both systemic treatments. Among patients treated with HT, 37 (61%) were given an aromatase inhibitor and 23 (38%) were given tamoxifen (one missing data). A GnRH analog was given to induce menopausal status in premenopausal women. Four patients received a GnRH analog without other endocrine compounds to protect ovarian function from CT-induced damage. All patients had already terminated adjuvant CT, when prescribed, before starting laser treatment, but almost all patients were still undergoing adjuvant HT, when required. Patients were required to discontinue previous VVA treatment at least 30 days before starting CO_2 laser therapy. Due to the observational and retrospective nature of this study, Ethics Committee approval was not required under Italian law.

Treatment strategy

Patients were treated with three cycles of fractional microablative CO_2 laser every 30 to 40 days, as usually recommended.[24,25,27] A basal gynecological clinical examination and Pap test were performed before starting the first course. Pap tests had to be negative. The following VVA symptoms were evaluated: vaginal laxity induced by estrogen deprivation, vaginal discharge, dryness, itching and/or stinging, vaginal bleeding, and dysuria. All women were sexually active, and were evaluated for dyspareunia and reduced sensitivity during sexual intercourse. We also evaluated laser-associated discomfort and procedure-related discomfort experienced during the insertion and manipulation of the laser probe. Both the severity of VVA symptoms and procedure-related discomfort were assessed with a visual analog scale (VAS) from 0 to 100, as described previously.[29] At each treatment cycle and 30 days after three cycles, patients underwent a gynecological clinical examination and reassessment of symptom severity using the above mentioned VAS scales. The fractional microablative CO_2 laser (SmartXide^{2}V^{2}LR; (MonaLisa Touch, DEKA, Florence, Italy) procedure was performed, as described elsewhere,[24] using the following settings: a dot power of 30 V, scan time of 1000 μs, dot spacing of 1000 μm, and the Smart Stack parameter from 1 to 3. The procedure did not require any preparation (eg, analgesia/anesthesia). Three gynecologists with the same level of skill performed the procedure using the same technique.

Statistical analyses

The mean VAS scores for each symptom were calculated at baseline (T0) and after completion of three cycles of treatment (T3). The mean VAS score for each procedure-related discomfort symptom was evaluated after the first and third cycles. Multiple *t* tests for pairwise comparisons were performed to determine the statistical significance of the difference between the mean VAS scores of each symptom before and after completion of three cycles. α error was set at 0.05; however, the Bonferroni correction was applied to establish the level of significance. Therefore, the results of univariate analyses were considered statistically significant at $P \leq 0.0083$ for VVA symptoms and $P \leq 0.016$ for procedure-related discomfort symptoms. For results that were significant at univariate analyses, we performed multivariable analyses with a linear regression model to assess the potential impact of age, baseline mean VAS scores, and type of adjuvant treatment (CT, HT, or both) on the final mean VAS scores. Statistical analyses were performed with the R software for MAC OS X, vers.3.4.0.[34]

RESULTS

All baseline Pap tests were negative. Five patients did not complete the three cycles of laser treatment. Three discontinued treatment after two cycles because of persistent procedure-related discomfort, whereas the other two patients discontinued after the first cycle for unknown reasons.

At baseline, almost all patients had sexual-related symptoms (88% reduced sensitivity during sexual intercourse and 98% dyspareunia) and genitourinary symptoms (56% vaginal laxity, referred to as ''a sense of heaviness'' at vaginal level, 60% vaginal discharge, namely, flatulence and/or leucorrhea, 94% vaginal itching/stinging, 68% vaginal bleeding, 65% dysuria, and 100% vaginal dryness). During the first laser cycle, 95% of patients reported pain during probe insertion, 94% reported pain during probe movements, and 87% reported laser-associated pain.

After three treatment cycles, there was a reduction in the number of patients suffering from both sexual-related symptoms (74% still reported reduced sensitivity during sexual intercourses and 80% dyspareunia) and genitourinary symptoms (43% of patients still suffered from vaginal laxity, 45% vaginal flatulence and/or leucorrhea, 65% vaginal itching/stinging, 45% vaginal bleeding, 41% dysuria, and 83% vaginal dryness). During the last cycle, 89% of patients reported pain during probe insertion, 87% reported pain during probe movement, and 83% reported laser-associated pain. Table 2 shows how the mean and range of VAS scores for each symptom differed before and after the completion of three cycles of laser therapy. As shown in Table 3, pre- versus post-treatment differences in the mean VAS scores were significant for sensitivity during sexual intercourse, vaginal dryness, itching/stinging, dyspareunia and dysuria ($P < 0.001$ for all), bleeding ($P = 0.001$), probe insertion ($P = 0.001$), and movement-related pain ($P = 0.011$). There was also a trend towards significance in the reduction of the mean VAS scores for vaginal discharge ($P = 0.0088$). The mean VAS scores for vaginal laxity and laser-related discomfort did not differ significantly between T0 and T3 ($P = 0.07$ and $P = 0.3$, respectively).

Figures 1 to 3 show the mean VAS scores at T0 and T3 of symptoms that changed significantly after laser treatment at univariate analysis. At multivariate analyses, adjuvant therapies significantly affected the final mean VAS score of probe movement-related pain in women who received both CT and HT ($P = 0.049$, adjusted $R^2 = 0.19$). The basal mean VAS score influenced the final mean VAS score for dysuria

TABLE 2. *Range and mean VAS scores for each symptom at baseline and after three cycles of CO_2 laser therapy*

	T0 (n = 82)		T3 (n = 77)	
VVA symptoms	VAS range	Mean	VAS range	Mean
Vaginal laxity	0-10	2	0-7	2
Reduced sensitivity during sexual intercourse	0-10	6	0-10	3
Vaginal discharge	0-10	3	0-8	2
Vaginal dryness	3-10	9	0-10	4
Vaginal itching/stinging	0-10	7	0-10	3
Vaginal bleeding	0-10	3	0-8	2
Dyspareunia	0-10	9	0-10	4
Dysuria	0-10	3	0-8	2
Technique Tolerability Symptoms	C1 (n = 82)		C3 (n = 77)	
Pain during probe insertion	0-100	40	0-90	30
Pain during probe movements	0-100	30	0-70	20
Laser associated-pain	0-80	30	0-90	30

All means are rounded.
C, cycle; N, number of patients; T, time; VAS, visual analog scale; VVA, vulvovaginal atrophy.

TABLE 3. *Differences in mean VAS scores before and after three cycles of CO_2 laser treatment*

VVA symptoms	Mean difference T3-T0	95% CI	*P*	% Reduction
Reduced sensitivity during sexual intercourse	3	2-4	<0.001	50%
Vaginal discharge	1	0-2	0.0088	33%
Vaginal dryness	5	4-5	<0.001	56%
Vaginal itching/stinging	4	3-4	<0.001	57%
Vaginal bleeding	2	1-3	0.001	33%
Dyspareunia	4	3-5	<0.001	56%
Dysuria	2	1-2	<0.001	33%
Procedure-related symptoms	Mean difference C3-C1	95% CI	*P*	% Reduction
Probe insertion-related pain	10	5-10	0.001	25%
Probe movement-related pain	10	0-10	0.011	33%

All means and 95% confidence intervals are rounded.
C, cycle; CI, confidence interval; T, time; VAS, visual analog scale; VVA, vulvovaginal atrophy.

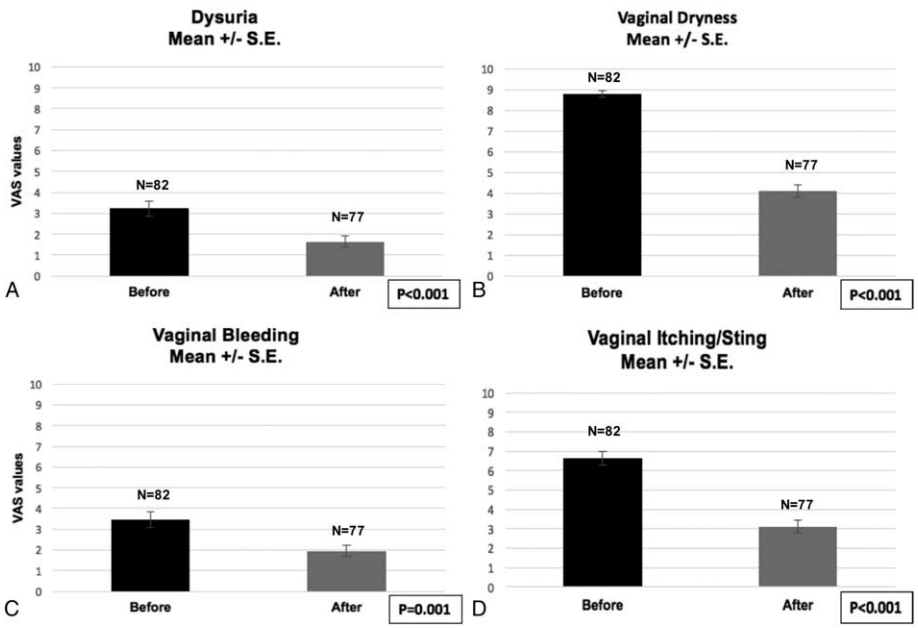

FIG. 1. Mean VAS score ± standard error for (**A**) dysuria, (**B**) vaginal dryness, (**C**) vaginal bleeding, and (**D**) vaginal itching/stinging before and after three cycles of fractional microablative CO_2 laser therapy. VAS, visual analog scale.

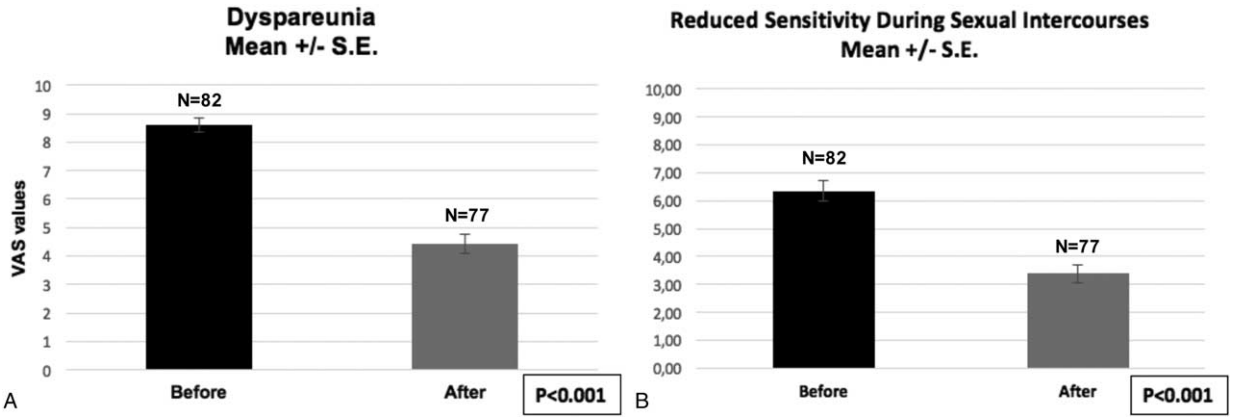

FIG. 2. Mean VAS score ± standard error for (**A**) dyspareunia and (**B**) reduced sensitivity during sexual intercourse before and after three cycles of fractional microablative CO_2 laser therapy. VAS, visual analog scale.

($P = 0.0008$, adjusted $P^2 = 0.17$), vaginal itching/stinging ($P = 0.003$, adjusted $R^2 = 0.09$), pain during probe insertion ($P < 0.0001$, adjusted $R^2 = 0.25$), and probe movement-related pain ($P = 0.003$, adjusted $R^2 = 0.19$). Age did not affect any symptom at multivariate analyses.

DISCUSSION

The results of this study reinforce our previous finding that fractional microablative CO_2 laser may be beneficial in the treatment of VVA in patients affected by BC.[28] Although symptoms were not completely relieved in many patients, the VAS scores of most symptoms (ie, sensitivity during sexual intercourse, vaginal dryness, itching/stinging, bleeding, dyspareunia and dysuria, and also probe insertion and movement-related pain) were significantly lower after treatment. Notably, the reduced number of patients suffering from VVA symptoms at the end of the three laser cycles, the differences observed in both VAS ranges and in the mean differences between T0 and T3 for almost all symptoms, plus informal feedback from our patients, strongly suggest that the improvements in VVA symptoms were clinically relevant. However, it is conceivable that more than three cycles might be needed to obtain better relief of such symptoms.

No patient reported systemic adverse effects of the laser treatment nor were any observed, which is consistent with previous studies.[24-28] Moreover, two of the three procedure-related discomfort symptoms, namely probe insertion and probe movement-related pain, were significantly lower after cycle 3 versus baseline. Therefore, although we did not conduct a safety study, we provide evidence of the safety and tolerability of fractional microablative CO_2 laser treatment. We also found that tolerability improved with treatment cycles, as witnessed by the significant reduction in mean VAS scores for two of the three technique-related symptoms. Importantly, multivariable linear regression analysis conducted to explore the role of potential confounding factors on treatment outcomes showed that the type of adjuvant systemic anticancer therapy did not seem to affect treatment outcome. Similarly, treatment efficacy was unrelated to the patient's age. Lastly, the final mean VAS scores of vaginal itching/stinging, dysuria, and probe movement and insertion-related discomfort were usually influenced by higher mean

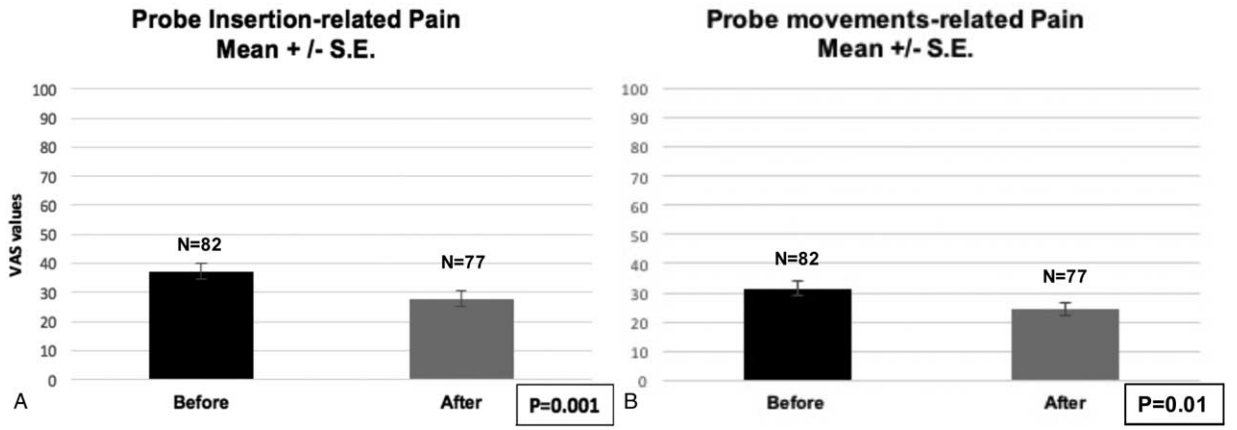

FIG. 3. Mean VAS score ± standard error for (**A**) probe insertion-related pain; and (**B**) probe movement-related pain, at baseline and during the third cycle of fractional microablative CO_2 laser therapy. VAS, visual analog scale.

basal VAS scores, which suggests that it might be useful to start the treatment when symptoms are less pronounced to achieve a greater reduction of symptom intensity.

CONCLUSIONS

To our knowledge, ours is the largest study conducted so far on BC patients treated with fractional microablative CO_2 laser therapy. It is also the study with the highest number of women undergoing laser treatment for symptoms of VVA. A limitation of this study is its retrospective nature. However, we were able to use multivariable analyses to assess the potential impact of some of the main confounding factors on the final mean VAS scores.

Three cycles of treatment did not relieve all patients of their symptoms; therefore, it is worth evaluating whether a greater number of cycles would be more effective. In addition, 1-year follow-up studies are required to address the issue of the duration of responses, and the need for retreatment. It would also be interesting to compare prospectively fractional microablative CO_2 laser therapy to other nonestrogenic local or systemic therapies in randomized trials to determine the best treatment, especially in the context of HR-positive BC, where estrogenic compounds are risky and therefore contraindicated.

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