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Original article

Vaginal laser therapy versus hyaluronic acid suppositories for women with symptoms of urogenital atrophy after treatment for breast cancer: A randomized controlled trial

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ABSTRACT

Background: Urogenital atrophy affects >50 % of women after breast cancer (BC) and there is reluctance to use local estrogen for this group. Hormone-free therapies like intravaginal laser therapy and hyaluronic acid suppositories have been shown to produce symptom relief in women with BC and urogenital atrophy, but have not been tested against each other. The aim of this study was to compare these nonhormonal modalities in women with urogenital atrophy after BC in a randomized fashion.

Study design: We randomly assigned 43 women (aged 49–58 years, mean age 54 years) with urogenital atrophy and a history of BC to receive intravaginal laser therapy (2 courses within 1 month) or hyaluronic acid suppositories (3 times/week continuously for three months). The primary endpoint was score on the Vaginal Health Index after 3 months. Secondary endpoints were subjective bother on a numeric rating scale for all urogenital atrophy domains, quality of life, sexual health and pelvic organ prolapse symptoms using validated questionnaires.

Results: Of the 43 women who participated, 22 were randomized to intravaginal laser therapy, and 21 to vaginal suppositories. At 3 months score on the Vaginal Health Index had improved significantly in both groups ($p = 0.001$), without a significant difference between treatment groups ($p = 0.232$). Significant improvement was also seen in both groups for subjective bother of urogenital atrophy, quality of life and sexual health, without significant differences between laser or hyaluronic acid therapy.

Conclusions: Both intravaginal laser therapy and hyaluronic acid suppositories are effective treatment options for women after BC suffering from urogenital atrophy. No difference was found between treatment regimens.

ClinicalTrials.gov identifier: NCT03816735, https://clinicaltrials.gov/ct2/show/NCT03816735

1. Introduction

Common concerns during menopause include vaginal dryness, burning, discharge, itching, sexual discomfort or pain and/or urinary symptoms of urgency and dysuria and occur in up to 50 % in postmenopausal women [1]. These symptoms are associated with estrogen deficiency related tissue changes of the vulva, vagina and lower urinary tract [2]. In clinical trials, dyspareunia and vaginal dryness are the most bothersome symptoms reported [3].

Especially in women after breast cancer (BC) treatment like chemotherapy or antihormonal therapy symptoms are even worse and the above listed symptoms occur in up to 75 % [4]. Due to the radical decrease of circulating estrogen biologic and clinical changes in the urogenital tissues, such as decrease of elastin, thinning of the epithelium, reduced vaginal blood flow, diminished lubrication, and decreased flexibility and elasticity further aggravate clinical bother. Estrogen therapy is the most effective treatment for urogenital atrophy, however many providers and patients are reluctant to use estrogen in this setting [5]. Urogenital atrophy symptoms will not resolve without treatment but will deteriorate over time; hence, a sufficient treatment is necessary

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to avoid negative impact on a woman's quality of life (QoL).

Nonhormonal treatment options for urogenital atrophy include vaginal lubricants or hormone free suppositories and laser therapy. Hyaluronic acid was effective to treat dryness, dyspareunia and urinary incontinence [6,7]. Hyaluronic acid is a natural substance that occurs in human tissue, which exhibits water-binding properties and thus regulates the moisture content of the tissue. The erbium-doped yttrium-aluminum-garnet (Er:YAG) laser is based on photothermic treatment of connective tissue by affecting collagen remodeling resulting in tightening of the supportive tissue [8–10]. Pilot studies of intravaginal microablative or non-ablative laser therapies with Erbium-YAG or CO2 lasers have demonstrated significant clinical improvement of urogenital atrophy and stress urinary incontinence [11,12]. Recent systematic reviews indicate that vaginal laser might be able to improve bothersome symptoms of urogenital atrophy [13] while it seems that in BC survivors the efficacy is even less [14]. Others have investigated hyaluronic acid-based liquid preparation for vaginal use [6,15].

The aim of this study was to compare intravaginal laser therapy with local hyaluronic acid in women with urogenital atrophy and a history of BC in a randomized fashion. (ClinicalTrials.gov number, NCT03816735).

2. Materials and methods

This is a single center, randomized controlled trial of patients with urogenital atrophy after BC.

Patients were recruited from follow-up BC clinics at our institution. Women with a history of BC and completed locoregional therapy were screened for urogenital atrophy and invited to participate in the study. Eligible patients had to report at least one of the following symptoms: vaginal dryness, burning or irritation; lack of lubrication during sexual intercourse/ sexual discomfort or pain; symptoms of urgency and dysuria; recurrent urinary tract infection. Exclusion criteria were current or past genitourinary malignancy, abnormal PAP smear, current genitourinary tract infection, abnormal uterine bleeding or the use of photosensitive medication.

After study inclusion patients underwent a gynecological examination, including completion of the Vaginal Health Index (VHI) to assess degree of atrophy and mucosal appearance. Both before treatment and 3 months later patients had a structured interview and filled out the below mentioned validated questionnaires.

Patients were randomly allocated to either intravaginal laser therapy or hyaluronic acid treatment using an online randomizer tool (www.randomizer.at). Laser treatments were performed with the Erbium:Yag Laser Juliet, MCL31 Dermablate (Asclepion Laser Technology GmbH, Jena, Germany). Before the procedure, the vagina was inspected and dried with a swab. The vaginal probe was inserted and laser parameters were set to Cold mode (Fluence 20 J/cm2). The probe was rotated and retracted using the graduated scale on the probe, resulting in a circular irradiation of the entire vaginal wall. The procedure was repeated using the Warm mode (Fluence 6 J/cm2). Laser application and parameters were used according to the manufacturer's recommendations. Patients were treated with 2 laser applications (at baseline and again 1 month later); a follow-up visit was performed 3 months after the initial treatment.

Patients randomized to the suppository group received Cikatridina vaginal suppositories (provided by the company Angelini). These suppositories include natural plant extracts from *aloe vera*, marigold, tiger grass and tea tree that are meant to support the wound-healing effect of hyaluronic acid and have an anti-inflammatory effect. The suppositories had to be applied vaginally daily during the first 10 days, and then every third day during the entire study period. Patients were asked to complete a diary to document days of suppository use. After study completion at 3 months, women were offered two laser treatments in case they were not satisfied with the suppository treatment.

The primary outcome parameter was the VHI score to evaluate the appearance of the vaginal mucosa (elasticity, pH, vaginal discharge, mucosal integrity and moisture) on a scale from 1 to 5 each [16] with a low score indicating vaginal atrophy.

Secondary outcome parameters were subjective bother of urogenital atrophy and degree of discomfort or pain during laser therapy using a numeric rating scale (NRS) ranging from 0 to 10 with 0 indicating no bother at all and 10 the highest bother possible. Further parameters were the Patient Global Impression of Improvement (PGI-I) [17] and Patient Global Impression of Severity (PGI-S) [18].

Quality of life (QoL) was determined by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (EORTC-QLQ-BR45) with higher values indicating better QoL [19]. Sexual health was determined with the female sexual health questionnaire with lower scores indicating better sexual health/less sexual health problems (EORTC SHQ—C22) [20]. Pelvic floor symptoms were determined using the validated Australian pelvic floor questionnaire [21] (translated and validated for German known as the "Deutscher Beckenboden- Fragebogen" [22]) also with lower scores being associated with less pelvic floor symptom bother. No clinical assessment in regard to pelvic floor muscle strength or incontinence was performed. However, self-report questionnaires have become a standard measure to assess treatment outcomes view. Treatment satisfaction was evaluated with the Zuf-8 questionnaire with higher scores being associated with high treatment satisfaction [23].

Adverse events included side effects of the vaginal treatment like vaginal burns, or allergic reactions to the suppositories. Serious adverse events were defined as any problems being fatal or life-threatening, leading to permanent damage, or rendering in-hospital treatment and had to be reported within 72 h after identification.

2.1. Sample size calculation

Gambacciani et al. (2015) found an increase of the VHI score from 10.6 ± 3.6 to 19.8 ± 1.3 in women treated with an Erbium:Yag Laser and from 11.2 ± 2.8 to 15.3 ± 1.5 in women treated with estriol gel after 12 weeks. Assuming comparable VHI/urogenital atrophy scores in our study, the sample size calculation based on a baseline score of 11 for both groups and an increase to a urogenital atrophy score of 19 and 15 in the laser therapy and vaginal hyaluronic acid therapy, respectively. A sample size of 20 patients in each group was needed to detect this different changes (interaction: $\alpha = 0.05$, $1\text{-}\beta = 0.90$) using a univariate two-group repeated measures analysis of variance. Theses sample size calculation is based on a common standard deviation of 4 and a correlation of measurements of $\rho ij = 0.4$. Assuming a dropout rate of approximately 10 % 22 patients in each group have to be included in this study, resulting in a total of 44 patients to be included.

2.2. Statistical analysis

Descriptive statistics are presented as median and interquartile range (IQR) for continuous variables and as counts and percentages for categorical variables. Questionnaire scales were calculated according to the questionnaire manuals and treated as continuous variables. Since responses to the many single item domains of the EORTC QLQ-BR45 only varied between two or three response categories the calculation of mean or median was not meaningful. Therefore the results for these single item domains are given as frequencies.

Changes within groups were analyzed using Wilcoxon signed-rank test and McNemar test, Differences between laser and suppositories were analyzed using Mann Whitney *U* Test, Chi-square Test or Fisher's exact Test. The level of significance is set to 5 %. SPSS 26.0.0.0 was used for data analysis.

The protocol was approved by the local ethics committee and the Austrian Federal Office for Safety in Health Care. All women gave written informed consent.

3. Results

50 women with urogenital atrophy after BC were screened and six had to be excluded for cervical dysplasia or untreated vulvar dermatosis; one was excluded after randomization because she was included even though untreated vulvar dermatosis was present. Hence, a total of 43 women were enrolled from January 2019 to December 2020. Table 1 shows baseline demographic and clinical characteristics for each group; no significant differences were seen between the two groups. Women with a history of BC were aged between 49 and 58 years with a mean BMI of 23. Two thirds of women had not had intravaginal treatments, and one third had used intravaginal treatments with various non-hormonal products in the past. Study participants were asked to cease any intravaginal treatment except the allocated study medication at time of study inclusion. Lubricants for sexual intercourse were allowed throughout the study. 22 women were randomized to the laser therapy group, 21 to the vaginal suppositories group, respectively.

3.1. Primary outcome

At baseline the mean VHI was 9 (8–13) in the laser groups vs. 13 (10–16) in the suppository group ($p = 0.031$), indicating vaginal atrophy in all study participants. The VHI improved significantly in both groups ($p = 0.001$) with no differences between treatment groups ($p = 0.232$).

3.2. Secondary outcomes

At baseline, vaginal dryness and dyspareunia were the most bothersome subjective urogenital atrophy symptoms affecting >80 % of women (Table 2). At 3 months, most subjective urogenital atrophy symptoms improved significantly without any significant difference between treatment type. Before the study, subjective vaginal atrophy was reported by 91 % and 86 % of women both in the laser and suppository group with a non-significant reduction to 73 % ($p = 0.219$) and 67 % ($p = 0.289$) at three months. The bother of vaginal atrophy on a NRS from 0 to 10 improved from 7 (3–8) to 3 (0–7) points in the laser group ($p < 0.001$) and from 4 (0–8) to 2 (0–4) in the suppository group ($p = 0.002$) in line with a significantly improved VHI scores in both groups.

88 % of study participants were sexually active at time of randomization with 32/35 (91 %) of women suffering from dyspareunia. While 100 % of sexually active women had dyspareunia before laser therapy only 80 % experienced dyspareunia after treatment. The related bother decreased from 9 (8–10) to 7 (5–10) ($p = 0.002$). While in the suppository group dyspareunia rate did not significantly decrease, the mean bother scores decreased from 7 (5–10) to 5 (0–8) ($p < 0.001$).

Most women reported symptoms of urinary incontinence according to the pelvic floor questionnaire; 12 % had overactive bladder (OAB) without urinary incontinence (OAB dry), 37 % overactive bladder with urinary incontinence (OAB wet) and 32 % stress urinary incontinence (SUI) with low bother scores for all types of urinary incontinence. No treatment arm was able to completely resolve subjective urinary incontinence symptoms, however, in both groups the bother of OAB symptoms decreased significantly [laser group: 0 (0–6) to 0 (0–0), $p = 0.016$; suppository group: 0 (0–4) to 0 (0–3), $p = 0.021$], respectively. In regards to SUI, the bother decreased only significantly ($p = 0.031$) in the laser group [laser group: 0 (0–4) to 0 (0–0), $p = 0.031$; suppository group: 0 (0–3) to 0 (0–2), $p = 0.063$].

PGI-S improvement was seen in the laser group while there was no significant change in the suppository group [laser group: 3 (2–3) to 2 (1–3), $p = 0.003$; suppository group: 2 (1–3) to 2 (1–2), $p = 0.101$]. The median PGI-I at 3 months was 3 in both groups (slightly better); the interquartile range was between 2 and 4 (better to no change) without a significant differences between groups ($p = 0.897$).

Treatment satisfaction in general was high in both groups with 20.5 (20.0–22.0) (laser group) and 20 (19–21) out of 32 points (supp. group) on the ZUF scale.

11/ 21 (ca 52 %) of women from the suppository group opted for a laser therapy after 3 months due to ongoing urogenital atrophy symptoms. We recommended suppository use after unsuccessful laser therapy, however, we do not have the data on the percentage of women who opted for ongoing suppository treatment in the laser group.

The results from the questionnaires mirror subjective and objective findings in regard to treatment success.

The EORTC QLQ-BR45 questionnaire showed significant improvement in several QoL domains like systemic therapy side effects, endocrine therapy symptoms skin, mucosis symptoms and sexual domains like sexual enjoyment, and endocrine sexual symptoms after laser therapy while the “sexual functioning domain” worsened. After suppository treatment, there were less pronounced differences with only QoL domains like systemic therapy side effects and endocrine sexual symptoms improving significantly (Table 3).

According to the EORTC SHQ-C22 only the multi-item domain sexual pain decreased significantly in the laser group from 62.5 (45.8–66.7) to 33.3 (25.0–50.0; $p = 0.001$) while it did not quite reach significance in the suppository group [58.3 (33.3–66.7) to 54.2 (8.3–66.7); $p = 0.055$]. The second multi-item domain sexual satisfaction did not improve significant throughout the study (Laser: $p = 0.051$, suppository group: $p = 0.082$). The remaining single-item domains did not reveal any significant changes after treatment and between treatment groups. Study participants had high scores in all subdomains indicating poor sexual health; hence data are shown in frequencies (Table 4).

Pelvic floor symptoms were assessed with the Australian Pelvic Floor Questionnaire. The overall score improved significantly in both groups (laser: 6.7 (4.7–9.0) to 5.4 (3.2–7.5); $p = 0.008$ and suppository group: 7.1 (6.2–9.3) to 5.9 (4.9–7.8); $p = 0.029$). However, similar to the remaining results, treatment groups were comparable at follow up ($p = 0.650$). As expected from the subjective bother score, the incontinence domain showed a significant improvement in the laser group [1.0 (0.4–2.1) to 1.0 (0.2–1.8); $p = 0.017$] but not in the suppository group [1.4 (0.7–2.1) to 1.1 (0.7–2.7); $p = 0.826$]. Conversely, the sexual health domain improved significantly in the suppository group [4.2 (3.3–4.8) to 3.3 (2.5–4.2); $p = 0.007$] but did not reach significance in the laser group [3.8 (3.3–4.2) to 3.3 (2.3–3.8); $p = 0.054$] (Table 5).

Table 1
Demographic data of patients (n = 43).

	Laser (n = 22)	Hyaluronic acid (n = 21)	Total (n = 43)	p-value
Age (years)	54 (48–58)	56 (49–58)	54 (49–58)	0.798
BMI (kg/m^2)	23.4 (21.2–26.1)	23.2 (22.4–25.3)	23.3 (21.6–26.0)	0.930
Parity [Median (Range)]	2 (0–3)	1 (0–2)	2 (0–3)	0.462
Hormonal status:				0.864
Premenopausal	4 (19.0 %)	5 (22.7 %)	9 (20.9 %)	
Postmenopausal	17 (81.0 %)	17 (77.3 %)	34 (79.1 %)	
Smoker:				0.488
No	21 (100.0 %)	19 (95.0 %)	40 (97.6 %)	
Yes	0 (0.0 %)	1 (5.0 %)	1 (2.4 %)	
Current AH therapy				0.086
AI	13 (61.9 %)	12 (57.1 %)	25 (59.5 %)	
Tamoxifen	1 (4.8 %)	6 (28.6 %)	7 (16.7 %)	
None	7 (33.3 %)	3 (14.3 %)	10 (23.8 %)	
Preceding vaginal therapy				0.123
No	16 (76.2 %)	12 (57.1 %)	28 (66.7 %)	
Yes	5 (23.8 %)	9 (42.9 %)	14 (33.3 %)	

Data are given as median and interquartile range (IQR) for continuous variables; and as counts and percentages for categorical variables. HA, hyaluronic acid; AH, antihormonal therapy; AI, aromatase inhibitor.

Table 2
Reported GSM symptoms at baseline and 3 months follow-up.

	Laser (n = 22)			HA (n = 21)			Laser vs HA at 3 Months
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value	p-value
Vaginal dryness	20 (90.9 %)	16 (72.7 %)	0.219	18 (85.7 %)	14 (66.7 %)	0.289	0.747
Bother on NRS	7 (3–8)	3 (0–7)	<0.001	4 (0–8)	2 (0–4)	0.002	0.411
Dyspareunia	19 (86.4 %)	15 (68.2 %)		16 (76.2 %)	13 (61.9 %)		0.907
Dyspareunia *	17/17	14/17	0.248	14/17	13/17	1.000	
Not sexually active	3 (13.6 %)	4 (18.2 %)	1.000	2 (9.5 %)	4 (19.0 %)	0.500	0.942
Bother on NRS	9 (8–10)	7 (1–9)	0.002	7 (5–10)	5 (0–8)	<0.001	0.216
OAB dry	7 (31.8 %)	3 (13.6 %)	0.125	9 (42.9 %)	8 (38.1 %)	1.000	0.088
OAB wet	3 (13.6 %)	0	n.a.	2 (9.5 %)	2 (9.5 %)	1.000	0.233
Bother on NRS	0 (0–6)	0 (0–0)	0.016	0 (0–4)	0 (0–3)	0.021	0.261
Recurrent UTIs	4 (18.2 %)	4 (18.2 %)	1.000	5 (23.8 %)	1 (4.8 %)	0.125	0.345
Bother on NRS	0 (0–0)	0 (0–0)	0.063	0 (0–0)	0 (0–0)	0.063	0.206
SUI	6 (27.3 %)	6 (27.3 %)	1.000	8 (38.1 %)	8 (38.1 %)	1.000	0.526
Bother on NRS	0 (0–4)	0 (0–4)	0.031	0 (0–3)	0 (0–2)	0.063	0.309

Data are presented as median (interquartile range, IQR). NRS, numeric rating scale; ranging from 0 to 10, OAB, overactive bladder; UTI, urinary tract infection; SUI, stress urinary incontinence. HA, hyaluronic acid; Dyspareunia * included only women who were sexually active at both timepoints.

Table 3
Quality of Life (EORTC-QLQ-BR45 questionnaire).

	Laser			HA			Laser vs HA
	Baseline (median)	Follow-up (median)	p-value	Baseline (median)	Follow-up (median)	p- value	p- value
Body image	75.0 (33 0.3–100.0)	75.0 (66.7–91.7)	0.752	75.0 (41.7–91.7)	75.0 (58.3–91.7)	0.380	0.536
Future perspective	33.3 (33.3–66.7)	66.7 (33.3–66.7)	0.071	50.0 (33.3–66.7)	66.7 (16.7–100.0)	0.763	0.806
Sexual functioning	16.7 (8.3–33.3)	33.3 (0.0–50.0)	0.004	33.3 (16.7–33.3)	33.3 (16.7–50.0)	0.150	0.677
Sexual enjoyment	100.0 (33.3–100.0)	33.3 (33.3–100.0)	0.023	83.3 (50.0–100.0)	50.0 (16.7–100.0)	0.160	0.897
Breast satisfaction	100.0 (83.3–100.0)	100.0 (83.3–100.0)	0.739	100.0 (66.7–100.0)	100.0 (50.0–100.0)	0.319	0.528
Systemic therapy side-effects	28.6 (19.0–38.1)	21.4 (14.3–38.1)	0.034	23.8 (14.3–33.3)	21.4 (11.9–23.8)	0.024	0.244
Upset by hair loss	33.3 (0.0–66.7)	33.3 (33.3–66.7)	1.000	16.7 (0.0–50.0)	33.3 (33.3–66.7)	1.000	1.000
Arm symptoms	27.8 (0.0–44.4)	22.2 (0.0–33.3)	0.742	22.2 (5.6–33.3)	11.1 (0.0–33.3)	0.110	0.639
Breast symptoms	33.3 (8.3–44.4)	16.7 (8.3–33.3)	0.496	25.0 (8.3–33.3)	16.7 (16.7–29.2)	0.887	0.822
Endocrine therapy symptoms	48.3 (22.2–63.0)	40.0 (25.9–43.3)	0.033	33.3 (20.0–50.0)	28.3 (16.7–54.4)	0.570	0.845
Skin mucosis symptoms	36.1 (22.2–44.4)	22.2 (11.1–33.3)	0.005	16.7 (0.0–33.3)	13.9 (0.0–27.8)	0.454	0.191
Endocrine sexual symptoms	83.3 (66.7–100.0)	50.0 (33.3–66.7)	<0.001	83.3 (66.7–91.7)	37.5 (9.7–66.7)	<0.001	0.362

Data are given as medians and IQR. HA, hyaluronic acid.

4. Discussion

Our study shows a significant improvement of any urogenital atrophy related symptoms both after treatment with intravaginal laser and hyaluronic acid suppository therapy with no difference between treatment groups.

Vaginal dryness and dyspareunia were found to be the most bothersome symptoms, which is in accordance with a recent systematic review [14]. Each of our vaginal therapies has shown similar effects in previous studies on its own [24,25]. We found significant improvements of presence and bother of these urogenital atrophy symptoms after three months of treatment. However, women still experienced bothersome problems after study completion, i.e. 50 % of women from the suppository group opted for a succeeding laser therapy due to ongoing urogenital atrophy problems. This is in line with recent systematic reviews; with vaginal laser therapy showing limited efficacy for the treatment of urogenital atrophy compared to placebo treatment [13,14,26,27].

There is a long list of factors that negatively impact on a woman's QoL after BC [28]. Sexual health is definitely an important aspect in women's QoL with and without BC. QoL according to the EORTC QLQ-BR45 questionnaire did not markedly improve after therapy, however, in the sexual domain women showed significant improvement after laser therapy. This is in line with our findings of the EORTC SHQ-C22 questionnaire where it seemed that laser therapy was superior in terms of sexual health, however, the study was not powered to answer this question.

Women with primary subjective SUI showed large variety in symptom improvement after vaginal laser therapy [29]. In our study laser therapy significantly reduced the subjective bother of SUI suggesting that laser therapy might be favorable in women with urogenital atrophy and coexisting urinary incontinence. In case of OAB any treatment of urogenital atrophy seems to improve symptoms according to the pelvic floor questionnaire. In any case, several pelvic floor symptoms improve after treatment of existing urogenital atrophy; however, the study was not powered nor was there any clinical examination performed in regard to urinary incontinence to allow final conclusions.

Table 4
Sexual Health (EORTC SHQ C22 questionnaire).

		Laser			HA			Laser vs HA
		Baseline (median)	Follow-up (median)	p-value	Baseline (median)	Follow-up (median)	p-value	p-value
Sexual satisfaction		23,4 (14,1-31,3)	28,13 (15,6-39,3)	0.051	31,3 (13,6-37,5)	31,7 (23,4-45,3)	0.082	0.388
Sexual pain		62,5 (45,8-66,7)	33,3 (25,0-50,0)	0.001	58,3 (33,3-66,7)	54,2 (8,3-66,7)	0.055	0.390
Importance of sexual activity	Not at all	2 (11 %)	2 (10 %)	0.228	0 (0 %)	0 (0 %)	–	0.149
	A little	2 (11 %)	5 (24 %)		0 (0 %)	1 (5 %)		
	Quite a bit	6 (32 %)	8 (38 %)		14 (74 %)	11 (55 %)		
	Very much	9 (47 %)	6 (29 %)		5 (26 %)	8 (40 %)		
Decreased libido	Not at all	0 (0 %)	1 (5 %)	–	2 (11 %)	1 (5 %)	0.392	0.742
	A little	0 (0 %)	4(20 %)		1 (5 %)	2 (11 %)		
	Quite a bit	4 (21 %)	7(35 %)		2 (11 %)	5 (26 %)		
	Very much	15 (79 %)	8 (40 %)		14 (74 %)	11 (58 %)		
Worry incontinence	Not at all	10 (53 %)	13 (72 %)	–	13 (65 %)	13 (65 %)	0.311	0.330
	A little	5 (26 %)	5 (28 %)		3 (15 %)	4 (20 %)		
	Quite a bit	2 (11 %)	0 (0 %)		4 (20 %)	3 (15 %)		
	Very much	2 (11 %)	0 (0 %)		0 (0 %)	0 (0 %)		
Fatigue	Not at all	2 (12 %)	3 (17 %)	0.406	5 (25 %)	7 (35 %)	0.156	0.283
	A little	7 (41 %)	3 (17 %)		2 (10 %)	6 (30 %)		
	Quite a bit	4 (24 %)	7 (39 %)		7 (35 %)	5 (25 %)		
	Very much	4 (24 %)	5 (28 %)		6 (30 %)	2 (10 %)		
Treatment effect on sexual activity	Not at all	1 (6 %)	7 (41 %)	0.197	0 (0 %)	7 (39 %)	–	0.929
	A little	1 (6 %)	2 (12 %)		1 (8 %)	4 (22 %)		
	Quite a bit	3 (19 %)	3 (18 %)		3 (23 %)	3 (17 %)		
	Very much	11 (69 %)	5 (29 %)		9 (69 %)	4 (22 %)		
Communication with professionals	Not at all	4 (27 %)	4 (22 %)	0.092	4 (24 %)	6 (33 %)	0.669	0.283
	A little	6 (40 %)	2 (11 %)		7 (41 %)	5 (28 %)		
	Quite a bit	4 (27 %)	8 (44 %)		5 (29 %)	3 (17 %)		
	Very much	1 (7 %)	4 (22 %)		1 (6 %)	4 (22 %)		
Insecurity with partner	Not at all	2 (13 %)	4 (21 %)	0.502	6 (33 %)	6 (32 %)	0.176	0.845
	A little	3 (19 %)	6 (32 %)		4 (22 %)	4 (21 %)		
	Quite a bit	6 (38 %)	6 (32 %)		7 (39 %)	5 (26 %)		
	Very much	5 (31 %)	3 (16 %)		1 (6 %)	4 (21 %)		
Vaginal dryness	Not at all	0 (0 %)	3 (16 %)	–	1 (6 %)	6 (35 %)	0.075	0.633
	A little	0 (0 %)	2 (11 %)		1 (6 %)	2 (12 %)		
	Quite a bit	4 (25 %)	7 (37 %)		4 (25 %)	5 (29 %)		
	Very much	12 (75 %)	7 (37 %)		10 (63 %)	4 (24 %)		
Treatment effect on body image	Not at all	5 (31 %)	7 (37 %)	0.287	5 (31 %)	9 (47 %)	0.221	0.929
	A little	4 (25 %)	6 (32 %)		5 (31 %)	5 (26 %)		
	Quite a bit	1 (6 %)	2 (11 %)		4 (25 %)	1 (5 %)		
	Very much	6 (38 %)	4 (21 %)		2 (13 %)	4 (21 %)		

Data are given as medians and IQR. HA Hyaluronic acid.

Table 5
POP symptoms (Pelvic organ prolapse questionnaire).

	Laser			HA			Laser vs. HA
	Baseline (median)	Follow-up	p-value	Baseline	Follow-up	p-value	p-value
Bladder function	0,98 (0,44-2,14)	1 (0,24-1,78)	0.017	1,37 (0,69-2,11)	1,11 (0,71 -2,67)	0.826	0,306
Bowel function	1,08 (0,61-2,22)	0,91 (0,30-1,67)	0.010	1,15 (0,61-2,03)	0,91 (0,61 -1,94)	0.069	0,722
Prolapse	0 (0,00-1,50)	0 (0,00-0,83)	0.070	0 (0,00−0,00)	0 (0,00-0,00)	0.500	0,139
Sexual function	3,75 (3,33-4,17)	3,33 (2,29-3,78)	0.054	4,17 (3,33-4,79)	3,33 (2,50-4,17)	0.007	0,895
Total	6,72 (4,66-8,99)	5,35 (3,24-7,47)	0.008	7,11 (6,16-9,29)	5,87 (4,88-7,75)	0.029	0,65

Data are given as medians and IQR. HA, Hyaluronic acid.

Several gynecological and similar societies have recommended vaginal laser therapy for urogenital atrophy only in the course of clinical studies due to unknown side effects [14,30,31]. No adverse effects have been reported in the course of this study similar to previous results. While there are almost no contraindications for the therapy with hyaluronic acid suppositories there are some that apply for laser therapy which needs to be taken into account when counselling patients.

Laser therapy treatment efficacy might be dependent on treatment regime. Sparse data are available on existing protocols [14]. Treatment success might improve after optimizing treatment protocols. In our study we only performed two laser treatments to avoid loss to follow-up or side effects in women with a history of BC. Further studies will be needed focusing on treatment regimens.

Salvatore et al. published one of the first papers to treat urogenital atrophy with a CO2 laser with significant improvement after 12 weeks [32]. The CO2 laser has also been investigated in the treatment of

urogenital atrophy in women with BC and similar to our data showed significant improvement of symptoms [33]. In our study, we opted for an Erbium:Yag Laser with a microablative mode instead of a CO2 laser due to the recent FDA warning about certain vaginal ablative laser therapy.

Similar to urinary incontinence it might be necessary to analyse the minimal important difference for women with urogenital atrophy to determine whether a treatment was successful or just statistically meaningful. Further research will be needed in this regard.

Strengths of this study were the randomized controlled design, and the comprehensive assessment of urogenital atrophy symptoms in various ways including subjective and objective outcome measurements with validated questionnaires being used.

A limitation of our trial is the relatively short follow-up. Long-term follow up was not evaluated through this study, since many women opted for laser therapy after they were allocated to suppository therapy in the first line and were not completely satisfied. Previous studies have suggested that recurrent treatment sessions may be necessary to maintain treatment effect in patients with urogenital atrophy, however, in our study only two laser treatments were available. Further studies will be needed to evaluate long-term results. Since the study was not designed to evaluate cross over therapy after 3 months and there was no funding to offer suppository treatment after initial laser therapy this could not be offered to our women. A slight bias might be present since the VHI score at time of randomization differed between treatment groups, however, we are unable to explain this finding since randomization was performed via an online tool without the possibility to influence randomization results. Since both treatment types are different, blinded randomization was not possible. Furthermore, it would have been difficult to design “placebo”-suppositories for the purpose of this study not to bias our results.

5. Conclusion

In conclusion, both intravaginal laser and suppository treatment appear safe and efficient for treatment of urogenital atrophy short-term in women with a history of BC. Long- term efficacy and safety need to be assessed.

Contributors

Daniela Gold contributed to study design, clinical duties, paper writing.

Laura Nicolay contributed to clinical duties.

Alexander Avian contributed to statistical analysis.

Elfriede Greimel contributed to study design, proofreading.

Marija Balic contributed to clinical duties, proofreading.

Gunda Pristauz-Telsnigg contributed to clinical duties, proofreading.

Karl Tamussino contributed to study design, proofreading.

Gerda Trutnovsky contributed to study design, clinical duties, proof reading.

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Ethical approval

The protocol was approved by the local ethics committee and the Austrian Federal Office for Safety in Health Care (30-225 ex 17/18). All women gave written informed consent.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

Declaration of competing interest

The authors declare that they have no competing interest.

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