THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

PAIN

Low-Level Laser Therapy for the Treatment of Provoked Vestibulodynia—A Randomized, Placebo-Controlled Pilot Trial

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ABSTRACT

Background: Low-level laser therapy (LLLT) is an emerging medical technology in which non-thermal laser irradiation is applied to treat pain. Because LLLT has been found effective in treating various pain syndromes without known side effects, we conducted a study evaluating the effect of LLLT on provoked vestibulodynia (PVD), a complex sexual pain disorder characterized by pain confined to the vulvar vestibule in response to contact or pressure.

Aim: To investigate the effectiveness of LLLT for PVD in a randomized, placebo-controlled, double-blinded trial.

Methods: Patients with PVD were randomly assigned to receive treatment with LLLT or sham treatment. Patients were treated twice weekly for 6 weeks, for a total of 12 LLLT or placebo sessions. Patients who showed improvement after LLLT were followed for 1 year by clinical pain report and Q-tip examination.

Outcomes: Change in pain scores obtained in response to the Q-tip test, clinical pain report, visual analog scale score, pain with tampon insertion, daily pain intensity, intercourse pain intensity, frequency of intercourse, and a battery of quality-of-life measures.

Results: Thirty-four patients with PVD participated, 18 received LLLT and 16 received placebo. In the clinical pain report at study completion, 14 of 18 patients (78%) receiving LLLT reported improvement compared with 7 of 16 (44%) in the placebo group ($P = .042$). This effect was not apparent in other outcome measurements. None of the patients reported side effects during the study. At 1-year follow-up, eight patients (57%) reported lasting improvement.

Clinical Implications: Larger studies with various treatment protocols are needed to define which patients can benefit from LLLT therapy.

Strengths and Limitations: Strengths include a placebo-controlled, double-blinded design, measurement of a large number of multidimensional end points, and a follow-up period of 1 year. Limitations include the small number of patients recruited, no improvement in measurable parameters, a high improvement rate in the placebo group, the absence of use of validated questionnaires, and the lack of evaluation of psychological and interpersonal factors that might have influenced the results.

Conclusions: Given the results of this pilot study, LLLT cannot currently be recommended as a treatment for PVD. Further studies with a larger population, various treatment protocols, and evaluation of LLLT in different subgroups of PVD are needed to define which patients can benefit from this therapy. **Lev-Sagie A, Kopitman A, Brzezinski A. Low-Level Laser Therapy for the Treatment of Provoked Vestibulodynia—A Randomized, Placebo-Controlled Pilot Trial. J Sex Med 2017;14:1403−1411.**

Key Words: Vulvar Pain; Provoked Vestibulodynia (PVD); Low-Level Laser Therapy (LLLT); Dyspareunia; Vulvar Vestibulitis

Received March 18, 2017. Accepted September 9, 2017.

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http://dx.doi.org/10.1016/j.jsxm.2017.09.004

INTRODUCTION

Provoked vestibulodynia (PVD) is defined as vulvar pain confined to the vestibule in response to contact or pressure.[1] Most patients with PVD present with dyspareunia and pain in response to non-sexual activities such as tampon insertion, gynecologic examinations, and even during sitting.[2] The diagnosis of PVD is made using the modified Friedrich criteria: a

history of vestibular pain upon touch or attempted penetration, tenderness to pressure localized within the vestibule on examination, and the exclusion of identifiable causes for the pain.[3]

The etiology of PVD remains unknown; proposed causes include chronic inflammation; peripheral neuropathy; genetic, immunologic, and hormonal factors; infectious processes; psychological disorders; sexual dysfunction; relationship factors; or disturbance in the central nervous system. However, given the varied presentation and individualized responses to treatment, the cause of PVD is most likely multifactorial. Because the exact mechanism of PVD remains unknown, many different treatment modalities have been proposed, including topical preparations (topical anesthetics, estrogen, compounded medications, and capsaicin), oral medications (tricyclic antidepressants and anticonvulsants), pelvic floor physical therapy, psychological interventions, and surgery ("vestibulectomy"), among others. There is a wide range of response to the various therapies, with 35% to 79% of women reporting some improvement in pain scores.[4] However, most published studies were case series, lacking a control or placebo group and lacking pretreatment pain and functional status evaluation, most used non-validated outcome measures of pain, and no long-term outcomes were reported.[4]

Regarding long-term results, it was shown that although most patients reported improvement since diagnosis,[5,6] they continued to experience a high level of symptoms[5] and only a small number of women reported that they were cured.[6,7] This long-term course has a profound negative impact on women's sexual, relational functioning, and psychological well-being.

Low-level laser therapy (LLLT) is a medical technology in which non-thermal laser irradiation (low levels of red and near infrared light) is applied to treat pain. It is referred to as "low level" or "cold" because a low-power laser is used in contrast to high-power laser therapy that is used for thermally coagulating tissues.[8] LLLT is non-invasive and painless and can be administered in primary care settings. The incidence of adverse effects is low, with no reports of serious events. Clinical applications that show effectiveness include soft tissue inflammation,[9] neck pain,[10] tendinopathies,[11] rheumatoid arthritis, and osteoarthritis.

The exact mechanisms of action for LLLT-mediated pain relief are not fully understood. Possible explanations include anti-inflammatory effects with a decrease of inflammatory markers (prostaglandin E_2, interleukin-1β, and tumor necrosis factor-α),[12] decrease of oxidative stress and skeletal muscle fatigue,[13,14] and inhibition of transmission at the neuromuscular junction, thus having a direct effect on myofascial pain and trigger points.[15] Another proposed theory posits a laser-induced neural blockade[16,17] and selective inhibition of peripheral nerve conduction, shown in Aδ and C fibers, which convey nociceptive stimulation.[18,19] These inhibitory effects could be mediated by disruption to fast axonal flow in neurons[17] or inhibition of neural enzymes.

AIMS

Because inflammatory mechanisms, peripheral neuropathy, and pelvic floor muscle dysfunction have been proposed in the pathogenesis of PVD, and LLLT is suggested to modify these factors, we studied whether LLLT might be an effective therapy for PVD.

METHODS

This pilot study was a placebo-controlled, double-blinded, randomized, clinical trial. Patients were recruited from the clinic for vulvovaginal disorders at our institution. The study was conducted from January 2011 through December 2013 and was approved by the institutional review board.

Inclusion criteria included more than 3 months of insertional dyspareunia and/or pain with tampon insertion and confirmation of vestibular tenderness by cotton-swab test, performed at five defined points in the vestibule (1, 5, 6, 7, and 11). In addition, patients verbally reported provoked pain intensity using a numeric rating scale ranging from 0 to 10 at the five points. The score for all points was summed together, and a total rating equal or greater than 10 of 50 was required for participation. Subjects had to be 18 to 50 years old; not pregnant; have no identifiable cause for pain, such as vaginitis, atrophy, dermatitis or dermatosis; and not using antidepressants or antiseizure drugs at recruitment.

After signing the informed consent form, patients underwent a standard evaluation that included a medical history, vulvar and vaginal examination, a pelvic floor musculature assessment, a vaginal culture, vaginal pH measurement, and microscopy. Each participant completed a questionnaire on demographics, general health, symptoms, and sexual functioning.

Instructions concerning the performance and documentation of the daily 24-hour pain diary and intercourse pain log were given at the first visit by the principal investigator.

During the trial, patients were allowed to use acetaminophen or non-steroidal anti-inflammatory drugs as pain "rescue medication" for indications other than dyspareunia. The use of topical anesthetics during intercourse was not allowed and was considered a protocol violation. Patients were required to stop any other PVD treatment 2 months before study initiation. In patients undergoing physical therapy at recruitment, treatment was stopped during the trial.

After completion of the LLLT or placebo treatment, participants were evaluated with a vulvovaginal examination, Q-tip test, and a battery of outcome measurements (see below).

Treatment With LLLT

Patients were randomly assigned to receive LLLT using the Omega XP diode laser system (Omega Laser Systems, Essex, UK) or placebo treatment. Treatment was performed with a pen-size probe transmitting irradiation applied to the vestibule for 20

seconds at each point. The irradiation parameters were wavelength of 820 nm, energy density of 32 J/cm^2, and pulsed light (alternating 73, 146, and 700 Hz). The placebo treatment was conducted in an identical manner using the same probe but without emitting irradiation. This was done using two possible options in the laser system, coded "A" and "B"; a specially designed switch allowed the operator to choose the required protocol. Because LLLT is not associated with heat, there was no difference in the sensation perceived by the patients in the two arms. The code was changed every 2 months by a non-blinded technician who was not involved in patients' recruitment or treatment. This coding system kept all study personnel completely blinded to the treatment arms during the trial.

The treatment protocol was based on clinical experience regarding tissue penetration and response to various protocols (recommended treatment doses for LLLT, revised in April 2010, World Association of Laser Therapy).[8,20,21]

Each painful location was treated by application of the probe; thus, the number of treatment points was defined according to each woman's physical examination. For example, a patient with vestibular pain located between 4 and 8 had five treatment points (4, 5, 6, 7, 8), and so forth. Patients were treated twice weekly by the same certified pelvic floor physical therapist for 6 weeks, for a total of 12 LLLT or placebo sessions.

Outcome Measurements

The primary outcome measurement chosen was the change in pain scores obtained in response to the Q-tip test. The test was performed at baseline and final visits in a standardized manner by the same investigator in all patients. It was carried out in a specific order (1, 11, 5, 6, 7) and patients verbally reported provoked pain intensity using a numeric rating scale, ranging from 0 to 10, at the five points.

The reported pain at all five points was summed together for comparison before and after treatment. Patients also were assessed with the Q-tip test at 3, 6, and 12 months after completion of treatment. Other outcome measures are described below.

Clinical Pain Report

At the final visit, women were requested to rate the level of pain during intercourse compared with the level of pain at recruitment using a 100-point pain scale. Improvement was defined as a decrease of at least 30 points (equal to 30%).[22] A reported decrease of less than 30% was defined as "no improvement," a 30% to 70% decrease of pain was defined as "moderate improvement," and more than 70% improvement was considered "great improvement."

Visual Analog Scale Measuring Discomfort in Daily Activities and Sexual Activity

A non-numerical rating scale measuring vulvar discomfort with the anchors "no discomfort at all" and "severe discomfort" was used to separately rate the severity of discomfort in daily activities and during sexual activity during the preceding week. The visual analog scale (VAS) score is presented as the absolute change from baseline (week 0) to the end of the trial (week 7).

Tampon Test[23]

Patients were instructed to insert a regular Tampax (Procter and Gamble, Cincinnati, OH, USA) tampon and immediately remove it by traction on the string. Patients rated the degree of pain during the entire insertion-removal maneuver on a 0 to 10 pain numeric scale. The tampon test is defined as the change of mean tampon-test pain of weeks 6 and 7 from the mean of weeks 0 and 1, labeled as baseline.

Daily 24-Hour Pain Measure and Intercourse Pain

Using a logbook, patients were requested to record daily whether they experienced vestibular pain and whether they attempted sexual intercourse (possible responses: 1 = "no, too painful," 2 = "no, not interested," 3 = "no, no opportunity," 4 = "yes"). If intercourse was attempted, the patient was asked to rate her level of pain on a 0 to 10 numeric scale. The data presented are the change of mean pain score at weeks 6 and 7 from weeks 0 and 1. The frequency of sexual intercourse is presented as the change of total times per week at weeks 6 and 7 from weeks 0 and 1.

Quality of Life and Sexual Function

Patients completed a questionnaire evaluating the extent to which PVD interfered with social activities, frequency of sexual intercourse, sexual desire, and becoming lubricated. It also included questions regarding frequency of discomfort during sex and satisfaction with overall sexual life. Data were acquired using a five-point numerical rating scale. Data are presented as "never" vs "any" interference or discomfort before the trial and at the end of the trial.

Patients also were asked to report any side effects they thought could be attributed to the treatment.

Long-Term Follow-Up

All patients in the placebo group were offered LLLT after completion of the study (Figure 1). Patients from the two arms who reported no improvement after LLLT were offered other treatments, including physical therapy, oral medications, psychological and sexual consultation, topical compounded creams, and vestibulectomy.

Patients who reported improvement after LLLT were followed for 1 year by Q-tip examination and were requested to report whether they found an improvement in their dyspareunia symptoms (yes or no).

Statistical Analysis

To compare quantitative variables between the two study groups, a two-sample t-test was applied. The association between

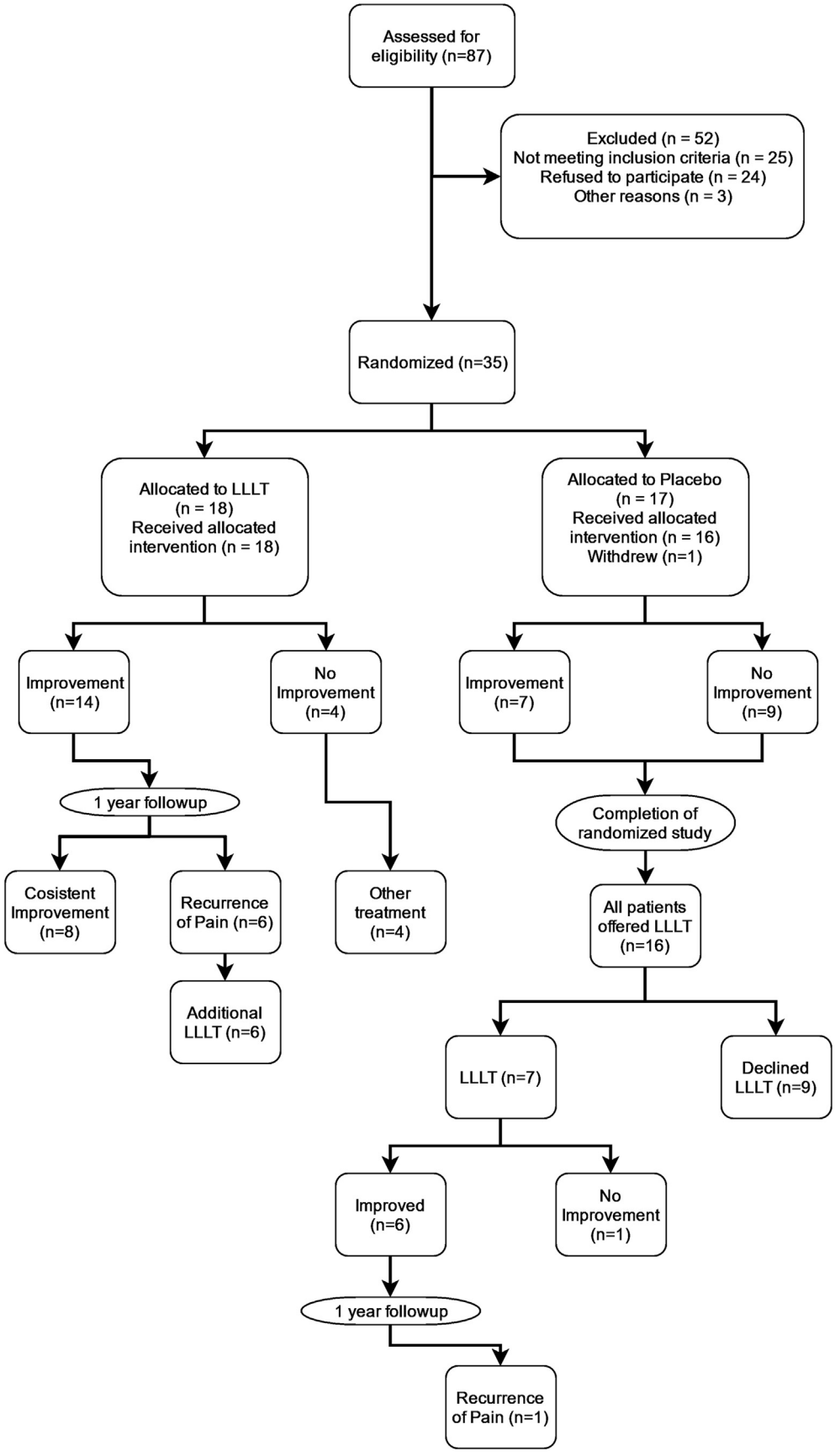

Figure 1. Distribution of participants throughout the study at baseline visit. LLLT = low-level laser therapy.

Table 1. Patient characteristics

	Range	LLLT (n = 18)	Placebo (n = 16)	*P* value
Age (y)	19–46	27.4 ± 5.8	25.4 ± 4.6	.296
Duration of pain (mo)	5 mo–20 y	86 ± 62.8	62.8 ± 54.9	.217
Currently married or partnered		83.3% (15)	69% (11)	.429
Nullipara		83% (15)	94% (15)	.604
Symptoms				
Discharge		22% (4)	6.3% (1)	.34
Itch		44% (8)	44% (7)	.968
Burning		50% (9)	56% (9)	.716
Dyspareunia		100% (18)	100% (16)	
Most bothersome symptom				.458
Dyspareunia		100% (18)	87.5% (14)	
Constant irritation		0	6.3% (1)	
Itch		0	6.3% (1)	
Pain starts after				.125
Intercourse		50% (9)	56% (9)	
Yeast infection		16.6% (3)	0% (0)	
Oral contraception		16.6 % (3)	0%	
Do not know		16.6 % (3)	44% (7)	
Primary PVD		61.1% (11)	68.8%	.642
Contraception method				.488
Hormonal contraception		39% (7)	56% (9)	
Condoms		33% (6)	19% (3)	
Other		11% (2)	6% (1)	
None		17% (3)	19% (3)	

LLLT = low-level laser therapy; PVD = provoked vestibulodynia.

two qualitative variables was tested using the χ^2 or Fisher exact test. The paired t-test was used for assessing the significance of change within each study group. The repeated measures analysis of variance model was used to simultaneously test the time effect, treatment effect, and the interaction between them. All tests applied were two-tailed, and a *P* value less than or equal to 0.05 was considered statistically significant.

RESULTS

Figure 1 presents the distribution of participants at the baseline visit. Eighty-seven women were screened and 62 met the entry criteria. Thirty-five consented to participate in the study, and 34 completed the randomized, blinded phase of the trial. One patient withdrew from the study after two appointments because of technical problems.

Of 34 patients who completed the study, 18 received LLLT and 16 received placebo. Patients' characteristics are presented in Table 1. The two groups were comparable in age, duration of pain, parity, contraception method, symptoms, and type of PVD (primary or secondary). All but one woman reported being heterosexual.

Patients reported receiving 0 to 10 different previous treatments (Table 2). The most common treatment was estrogen cream (73%), followed by pelvic floor physical therapy (70%), topical anesthetics (62%), antifungals (62%), topical steroids (38%), topical antibiotics (32%), probiotics (26%), acupuncture (9%), low-oxalate diet (9%), amitriptyline 2% and baclofen 2% cream (9%), and vestibulectomy (6%).

None of the patients reported side effects during the study. In the clinical pain report at study completion, 10 women in the treatment group reported "significant improvement" (>70% improvement), 2 reported "moderate improvement" (30–70%), and 2 reported "complete improvement" (total = 14 of 18,

Table 2. Previous treatments

	LLLT	Placebo	Total study group
Total treatments before study	4.52 ± 2.5	4.56 ± 2.6	*P* = .971
Antifungal	9	12	62%
Estrogen cream	14	11	73.5%
Topical antibiotics	7	4	32%
Steroid cream	7	6	38%
Pelvic floor physical therapy	11	11	70%
Topical anesthetics	10	11	62%
Probiotics	7	2	26%
Oral antidepressants	1	2	9%
Vestibulectomy	1	1	6%

LLLT = low-level laser therapy.

78%). Four women reported "no improvement" (<30%). In the placebo group, five patients reported "significant improvement," two patients reported "moderate improvement" (total = 7 of 16, 44%), and nine patients (56%) reported "no improvement" (P = .042; Table 3). The number of previous treatments did not affect the outcome on clinical pain in the treatment or placebo group (data not shown).

In contrast to the patients' clinical pain report, measurable parameters did not show a difference between groups. Comparison of the Q-tip test, intercourse pain on the VAS, and tampon tests before and after treatment showed a similar decrease of pain in the two groups (Table 3). There was no significant influence on frequency of intercourse in either group. In addition, no significant difference was found regarding the severity of discomfort in daily activities and/or in daily pain intensity in either group.

The extent to which PVD interfered with social activities, frequency of sexual intercourse, desire, lubrication, and sexual satisfaction did not differ before and after the treatment in either group (Table 4).

The 14 patients in the LLLT group who reported an improvement were followed for 1 year after completion of the treatment. On follow-up, eight patients (57%) reported lasting improvement after 1 year. The "complete improvement" that was reported by two women at the end of the study was maintained at the 1-year follow-up. Four patients who reported "significant improvement" remained satisfied with the results.

The remaining six patients (33%) who reported "significant improvement" at the end of LLLT reported recurrence of vestibular pain and requested additional treatment. They underwent repeated LLLT treatment (four to six sessions each) with significant improvement.

Q-tip examination assessed 1 year after completion of the study showed a significant decrease in pain scores, from 28.5 (SD = 9.9) to 21.2 (SD = 12.1; P = .024). Positive correlations were observed between a higher level of symptom decrease (delta before and after the treatment) and the level of current pain obtained after 1 year. This was noted for the VAS score measuring discomfort in sexual activity (r = 0.600, P = 0.008) and the sexual pain reported in the logbook (P = .036).

All patients in the placebo group were offered LLLT after study completion. Nine of 16 (56%) declined the LLLT; of the seven patients who received it, five patients reported "significant" or "complete improvement" and one reported "moderate improvement" (six of seven, 86%). In five patients, this improvement persisted for 1 year. One patient had improvement immediately after the treatment but reported recurrence of symptoms after several months, whereas one other patient had no improvement.

DISCUSSION

The aim of this randomized, placebo-controlled, double-blinded trial was to investigate the effectiveness of LLLT for PVD.

Table 3. Comparison of outcome measures between LLLT and placebo groups

	LLLT before	LLLT after	LLLT group, difference	Placebo before	Placebo after	Placebo group, difference	P value
Verbal report of improvement		14 (78%)			7 (44%)		.042
Q-tip test	28.50 ± 10	22.18 ± 13.6	6.3 ± 2.8 (22%)	29.06 ± 11.5	22.06 ± 13.4	7 ± 9.1 (24%)	.954
Sex pain—VAS	90.1 ± 8.3	64.7 ± 26.8	25.4 ± 22.7 (28%)	83.5 ± 19	61.5 ± 30	21.9 ± 27.3 (26%)	.467
Tampon test	4.4 ± 2.7	3.2 ± 2.1	1.16 ± 1.81 (36%)	3.4 ± 2.6	2.6 ± 2.6	0.75 ± 1.02 (22%)	0.395
Everyday VAS	9.5 ± 14.97	7.9 ± 19.82	1.12 ± 5.7 (11%)	27.58 ± 32.5	19.3 ± 29.09	8.3 ± 25.17 (35%)	.386
Daily vulvar pain intensity	1.39 ± 1.63	1.01 ± 1.51	0.386 ± 0.24 (27%)	2.48 ± 3.53	2.02 ± 3.18	0.6 ± 0.91 (24%)	.912
Intercourse frequency	2.5 ± 2.09	2.39 ± 1.72	0.11 ± 0.43 (−4%)	2.57 ± 2.03	2.39 ± 2.79	0.18 ± 2.13 (−7%)	.871
Pain level during intercourse (according to diary)	6.4 ± 1.98	5.64 ± 2.57	0.9 ± 1.94	6.441 ± 2.37	5.91 ± 2.44	0.10 ± 1.99	.245

LLLT = low-level laser therapy; VAS = visual analog scale.

Table 4. Study outcome regarding quality of life and sexual function domains

	LLLT before		LLLT after		Placebo before		Placebo after		*P* value
	A	N	A	N	A	N	A	N	
Interference with social activities	3 (17%)	15 (83%)	4 (22%)	14 (78%)	7 (47%)	8 (53%)	6 (37.5%)	10 (62.5%)	.69
Interference with frequency of sexual intercourse	16 (94%)	1 (6%)	11 (85%)	2 (15%)	12 (80%)	3 (20%)	13 (81%)	3 (19%)	1.0
Interference with sexual desire	15 (94%)	1 (6%)	14 (78%)	4 (22%)	11 (69%)	5 (31%)	8 (50%)	8 (50%)	.375
Difficulties with lubrication	14 (82%)	3 (18%)	13 (81%)	3 (19%)	11 (85%)	2 (15%)	12 (80%)	3 (20%)	1.0
Frequency of discomfort or pain during sex	17 (100%)	0 (0%)	12 (80%)	3 (20%)	14 (93%)	1 (7%)	12 (80%)	3 (20%)	.87
Satisfaction with overall sexual life	11 (69%)	5 (31%)	10 (59%)	7 (41%)	8 (44%)	10 (56%)	13 (87%)	2 (13%)	.507

A = any interference (always, most times, sometimes, and a few times); LLLT = low-level laser therapy; N = never or almost never.

According to patients' verbal report, LLLT effectively decreased symptoms of PVD in the majority of the treatment group compared with the placebo group. However, this effect was not apparent when all other measurable outcome parameters were evaluated immediately after completion of treatment. We cannot account for this discrepancy, and this sole significant effect could be a chance finding. Alternatively, the measurable parameters used in this study might not reflect the clinically significant status of sexual pain. Nevertheless, 57% of patients who reported improvement after LLLT experienced a consistent decrease in symptoms during the year after treatment, with a significant decrease in Q-tip examination pain scores, and most did not seek further treatment, thus supporting an actual improvement. In addition, the initial verbal report improvement rate of 78% with LLLT is comparable to the median improvement effect of vestibulectomy surgery reported in PVD trials.[4]

Although 78% of the LLLT group reported improvement, so did 44% of the placebo group. This placebo effect is similar to that reported previously with PVD in randomized clinical trials of non-surgical interventions, which showed 40% to 50% improvement rates in the placebo groups.[24–28]

The improvement noticed in the placebo group can be attributed to several factors, including the application of the probe to multiple points in the vestibule, causing soft tissue manipulation and desensitization, and a therapeutic effect of the two-weekly appointments with the physical therapist, with probably greater attention to the woman's pain and emotional distress, and this effect can reflect a spontaneous improvement of PVD, as has been observed in a longitudinal population-based study.[29]

However, the long-term improvement of the placebo groups was not evaluated, because patients were offered LLLT after completion of the trial.

The LLLT treatment regimen chosen for the study was based on accepted protocols for musculoskeletal and neuropathic pain syndromes. Data on LLLT are largely empirical; its physiologic mechanisms are not well understood and tend to be very broad.[30] One hypothesis is that LLLT increases the nociceptive threshold, specifically inhibiting A and C nerve fibers by the alteration of axonal flow[17] or by inhibition of neural enzymes.[31] In clinical practice, a large number of parameters, such as the wavelength, fluence, power density, and pulse structure, must be chosen for each treatment.[8] Decreased response or ineffective treatment could be the result of an inappropriate light source and dosage. Commonly in clinical practice, parameters are changed according to individual patient response, thus allowing a more individualized treatment regimen for every patient. Because of the placebo-blinded design of the study, we instituted a universal treatment protocol in which the same parameters were used for all treatments for all participants. A flexible protocol, with changing technical parameters according to patients' individual responses, or more than 12 sessions, could have achieved a superior response rate, and this should be evaluated further. In addition, it

is common to retreat patients with attenuation of the LLLT response; repeated treatment usually includes fewer interventions than in the primary program and can be provided as needed. In fact, after completion of the study, some patients who reported recurrence of vestibular provoked pain opted to repeat LLLT treatment, with marked improvement. The number and timing of additional LLLT sessions also should be determined in future studies.

Another possible explanation for the partial response rate is that PVD is a group of distinct disorders that have been classified together owing to common symptoms.[32] LLLT might be effective for only a subset of patients, and differences in response might represent different etiologic factors or diverse pain mechanisms. Analysis of successful vs unsuccessful treatment showed no differences between groups in age, number of previous treatments, or type of vestibulodynia (primary or secondary). When the exact etiology of PVD is identified or better classified, allocation of patients to specific treatment modalities, including LLLT, will be improved, thereby increasing the response rate.

The results of the study are limited by the small number of patients recruited. We observed a statistically significant difference only in the verbal report, whereas other measurable parameters did not show any differences. Other weaknesses include the absence of the use of validated questionnaires and the lack of evaluation of the psychological and interpersonal factors that might have influenced the results. In addition, there was a high improvement rate in the placebo group, further blurring the possible benefit of the treatment.

Despite these limitations, our study stands out from most previously published PVD clinical trials because we adopted a placebo-controlled, double-blinded design, measured a large number of multidimensional end points, and followed patients for 1 year, showing a prolonged beneficial effect.

Given the results of this pilot study, which showed statistically significant improvement in clinical pain report but did not meet the primary end point and five of six secondary end points, LLLT does not prove superiority over placebo. Therefore, LLLT cannot be currently considered an effective treatment for PVD.

Further studies with a larger population, flexible treatment protocols, and evaluation of different subgroups of PVD are needed to define the role of LLLT in the treatment of PVD.

ACKNOWLEDGMENT

The authors thank Omedic, Ra'anana, Israel, for providing the LLLT equipment.

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Conflicts of Interest: The authors report no potential conflicts of interest.

Funding: Marinoff Vulvodynia Career Development Award, National Vulvodynia Association.

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