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PAIN

Low-Intensity Shockwave for Treatment of Vestibulodynia: A Randomized Controlled Therapy Trial

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ABSTRACT

Background: Provoked vestibulodynia (PVD) is an exhausting pain syndrome that immensely affects quality of sexual life and consequently negatively affects quality of life. Low-intensity shock wave therapy produces physical forces that lead to pain relief.

Aim: The aim of this study was to evaluate the feasibility, safety, and efficacy of low-intensity shockwave therapy in patients with provoked vestibulodynia.

Methods: This is a double-blinded, randomized, sham-controlled, prospective study of 32 women. The treatment protocol included a series of treatments, performed twice a week for 6 weeks. Each treatment consisted of 500 pulses of low intensity shockwaves (0.09 mJmm2) using the Medispec, ED-1000 shockwave generator or sham. Participants were assessed at the baseline, and at 1 and 3 months after completing all treatments.

Outcomes: Pain was assessed by both subjective and objective measures. The primary outcome was a change in dyspareunia, as assessed by scores on the 10-point visual analog scale. Secondary outcome measures were changes in pain threshold and tolerance, assessed by a quantitative validated algometer test, the Wong-Baker pain FACES scale, the Female Sexual Function Index and the Patients' Global Impression of Change scale.

Results: From the baseline to 1 month and 3 months after completion of treatment, visual analog scale scores for dyspareunia decreased (8.0 ± 1.4, 5.7 ± 2.3, and 4.4 ± 2.5, respectively, $P < .005$). For these respective time points, Wong-Baker scores decreased (4.0 ± 0.6, 2.9 ± 1.2, 2.5 ± 1.3, respectively, $P < .05$); and total Female Sexual Function Index increased (17.9 ± 6.3, 20.9 ± 6.2, 22.5 ± 8, respectively, $P < .002$). Pain threshold and tolerance measured by the algometer were increased 3 months after completion of the treatment compared with the baseline (69.8 mmHg ± 11.8 vs 22.9 mmHg ± 9.0, $P < .01$ and 87.7 mmHg ± 35.7 vs 43.3 mmHg ± 14.7, $P < .0001$, respectively). No changes were observed in any of the measures assessed in the sham group.

Clinical Implications: We found a new effective treatment for alleviating the most bothersome symptom in PVD, pain during penetration and intercourse. This resulted in improved sexual function.

Strengths & Limitations: The strengths of this study are the randomized controlled design, the correlated subjective questionnaires, and the use of semiquantitative algometer methodology. The limitations are the relative low number of participants in a single center.

Conclusion: For women with PVD, low-intensity shockwave therapy applied at the introitus is a feasible, safe, and effective treatment option that may have a beneficial effect in pain relief and in sexual function. **Gruenwald I, Gutzeit O, Petruseva A, et al. Low-Intensity Shockwave for Treatment of Vestibulodynia: A Randomized Controlled Therapy Trial. J Sex Med 2021;18:347–352.**

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Key Words: Low-intensity shockwave therapy; vestibulodynia; pain; dyspareunia; sexual function

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INTRODUCTION

Vulvodynia is a chronic vulvar pain condition that affects as many as 28% of women during the course of their lifetime.[1] Provoked vestibulodynia (PVD) is the most common subset of vulvodynia and is the most common cause of dyspareunia in premenopausal women, affecting 12% of premenopausal women.[2,3] PVD is characterized by severe pain on minimal vestibular contact, hypersensitivity to a gentle cotton-swab test at the vestibular area, and vestibular erythema.[4] The pathophysiology of PVD is currently unknown. 2 of the most commonly proposed hypotheses include increased innervation and sensitization of nociceptors and thermoreceptors, and increased site-specific inflammatory responses.[1,5,6] The etiology is multifactorial, and over the years, only few etiologic factors have been thoroughly investigated, among them: oral contraceptive pills, candidiasis, and increased tonus of pelvic floor muscle.[1,4,5,7,8] First-line therapy for PVD includes one or a combination of local and systemic medications (i.e., analgesics, local estrogen, antidepressants), physical therapy, cognitive behavioral therapy, and acupuncture.[1,4,5,9,10] The efficacy of these conservative treatment options is unclear and more research is needed to confirm their beneficial effect. When conservative treatment is not satisfactory, surgical treatment can be offered. Vestibulectomy, surgical removal of the vestibule, is the most effective PVD operative therapy, but owing to the high rate of postoperative complications, mainly bleeding and wound infection, and in rare cases persistent severe vulvar pain, the referral rate to surgery is low.[11−13]

Extracorporeal shockwave therapy was first introduced in 1980 for nephrolithotripsy, and rapidly revolutionized the treatment of patients with kidney stone disease. This methodology has since been used at various intensities and has been applied in many medical fields (wound healing, cardiology, orthopedics),[14] with various success rates. In the past decade, this technique has been successfully used in the low-intensity range in the urologic field of erectile dysfunction.[15] To our knowledge, this is the first study to report the use of low-intensity shockwave therapy (LISWT) in women with PVD. Our primary aims were to examine its feasibility, safety, and efficacy in this population.

MATERIALS AND METHODS

The study was a single-center, double-blinded, randomized, sham-controlled, prospective study. Study eligibility criteria were treatment at the Neuro-urology Unit in Rambam Medical Center, during January 2018 − January 2020 and a diagnosis of PVD. PVD diagnosis was based on description of the pain and on a positive cotton-swab test.[16]

Women were randomized at a 2:1 ratio to treatment or sham groups. Determination of whether a patient would be treated by sham or by energy delivery was made by reference to a statistical series based on random sampling numbers drawn up for each probe (A,B,C), where probe A was the sham probe. The details of the series were unknown to any of the investigators. After enrolling the patient, the appropriate numbered envelope that was assigned to the number of the patient was opened at the clinic by the investigator. The letter written on a card inside the envelope determined if the patient was to be treated with an A, B, or C probe. The treatment protocol included a series of treatments, performed twice a week for 6 weeks, for a total of 12 sessions. Each treatment consisted of 500 pulses of low-intensity shockwaves (0.09 mJmm2) using the Medispec, ED-1000 shockwave generator. The sham protocol included the same treatment protocol without shockwave generator activation. The patients were evaluated 3 times throughout the trial by an investigator blinded to the group allocation: before the first treatment, and 1 and 3 months after the twelfth treatment. Pain was assessed by both subjective and objective measures. The primary outcome measure was a change in dyspareunia after shockwave treatment 3 months after the treatment compared to the baseline, as assessed by scores on the 10-point visual analog scale (VAS) (range 0-10).

Secondary outcome measures for evaluating pain were increases in pain threshold and tolerance, assessed by a quantitative validated algometer test,[17,18] the Wong-Baker pain FACES scale (range 0-10),[19] the Female Sexual Function Index (FSFI; Supplementary File 1) (range 2-38)[20] and the Patients' Global Impression of Change scale (PGIC; Supplementary File 2) (first component range 0-7; 0 = no change, 7 = a great deal better; second component range 0-10; 0 = much better and 10 = much worse).[21] The PGIC assessed the self-reported impression of a general change due to the intervention.

The algometer we applied was a very basic and simple device that we assembled and used at our unit after validating its safety, accuracy, and adequacy in evaluating introital pain vs control (doctorate dissertation). For assessing the pain threshold with the algometer, we applied radial pressure (mmHg) by progressively inflating a cylindrical balloon inserted in the introitus. The participant was required to report the first painful sensation. The measurement was performed sequentially 4 times and the average of the measured pressures was considered the first pain threshold. Finally, for pain tolerance measurement, the participant was again asked to report when she had reached her pain limit (0-10 on VAS) on continuous pressure (Figure 1).

Statistical Analysis

For data management and statistical analysis, SPSS version 27.0 for Windows (SPSS, Chicago, IL, USA) was used. Histograms were used to evaluate normality distribution of continuous parameters. The paired t-test and Wilcoxon sign rank test were used to compare continuous, normal, and non-homogenous distributed parameters as appropriate. For comparisons between the study and control groups, the independent Student t-test and Mann-Whitney test were used. The Pearson correlation was used to evaluate univariate linear correlation. A 0.05 significance level was used for all statistical tests. All tests were two-sided. This trial is registered in clinicaltrials.gov, number NCT04545255.

Figure 1. Low-pressure cylindric algometer. Figure 1 is available in color online at www.jsm.jsexmed.org.

POWER ANALYSIS

We used http://statulator.com program which calculated sample size for paired differences. With power of 80% and level of significant of 5%, for detecting a mean of the differences of VAS scale of 1.5 (20%) between pairs, assuming the standard deviation of the differences to be 2 we will need to recruit 17 participants.

RESULTS

Of 36 women assessed for eligibility, 2 declined participation. The remaining 34 women were randomized, 24 to the LISWT group and 10 to the sham group. One woman from each group was excluded from the analysis because of loss of follow-up (Figures 1 and 2). The final analysis included 32 women: 23 in the LISWT group and 9 in the sham group. Baseline characteristics, specifically age, duration of PVD, the proportions of primary and secondary PVD, history of sexual harassment, past PVD treatment, and contraceptive use were similar between the study groups with normal distribution (Table 1).

Efficacy

Visual Analog Scale

Baseline dyspareunia VAS score did not differ between the LISWT and the sham groups (8.00 ± 1.42 and 8.66 ± 1.65, respectively, $P = .25$). For the LISWT group, VAS scores for dyspareunia decreased from the baseline to 1 month and 3 months after completion of treatment (8.00 ± 1.4, 5.70 ± 2.3, and 4.40 ± 2.5, respectively, $P < .005$). No differences in dyspareunia VAS scores

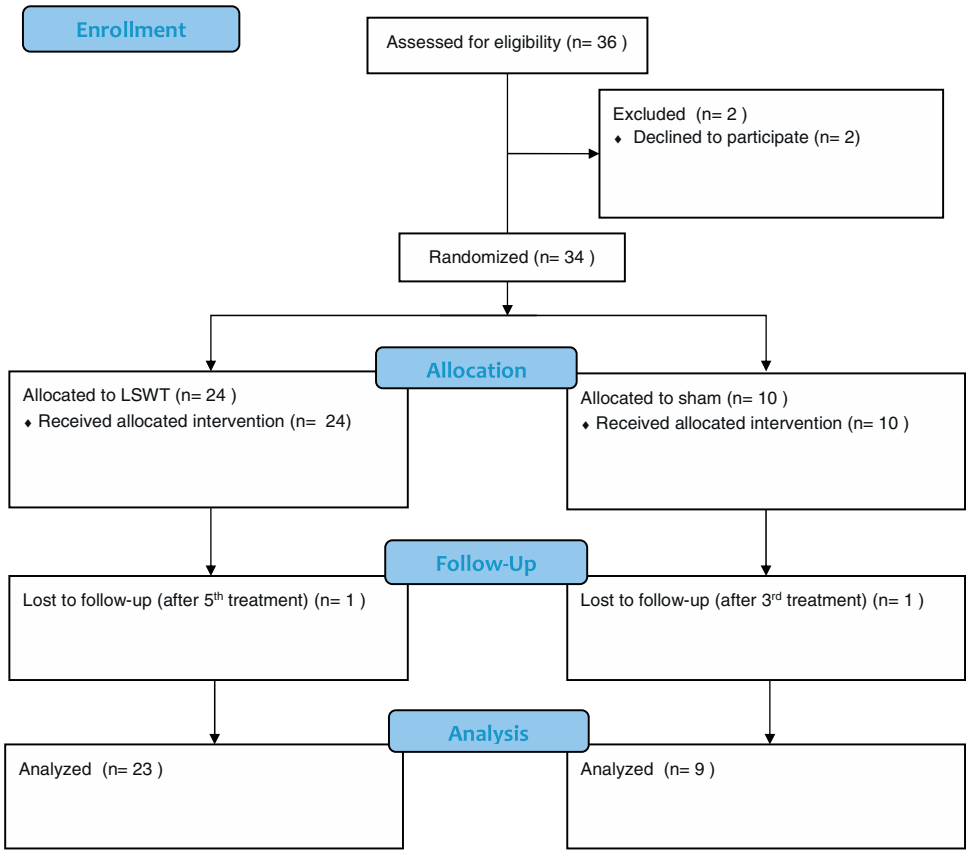

Figure 2. Subject enrollment flow diagram. Figure 2 is available in color online at www.jsm.jsexmed.org.

Table 1. Demographic characteristics

	Sham n = 9	LISWT n = 23	*P* value
Age [mean ± StD (Years)]	25 ± 9.29	27 ± 8.33	NS
Duration of PVD [mean ± StD (Years)]	4.2 ± 3.30	6.9 ± 8.65	NS
Primary PVD	5 (56%)	15 (65%)	NS
Secondary PVD	4 (44%)	8 (35%)	NS
Sexual harassment	9 (100%)	18 (78%)	NS
Past PVD treatment	7 (78%)	18 (72%)	NS
Contraceptive use	6 (67%)	9 (39%)	NS

Data are presented as means and standard deviations or as numbers (%).
LISWT = low-intensity shockwave therapy; PVD = provoked vestibulodynia.

were observed in the sham group between the 3 time points (8.66 ± 1.65, 8.30 ± 1.6, and 7.90 ± 2.2, respectively, $P = .174$).

Algometer

We used this quantitative methodology for assessment of pain threshold and tolerance. Baseline threshold and tolerance did not differ between the treated and the sham groups (22.5 mmHg ± 10.2 vs 22.9 mmHg ± 9.0, $P = .34$ and 43.3 mmHg ±14.7 vs 40.6 mmHg ± 13.21, $P = .27$, respectively). Pain threshold and tolerance were increased significantly 1 month after the twelfth treatment compared with the baseline (34.7 mmHg ± 18.8 vs 22.9 mmHg ± 9.0, $P = .062$ and 56.8 mmHg ± 22.0 vs 43.3 mmHg ±14.7, $P = .001$, respectively). Pain threshold and tolerance values in the sham group did not differ at the 1 month follow-up compared with the baseline (26.9 mmHg ± 10.3 vs 22.5 mmHg ± 10.22, $P > .05$ and 43.8 mmHg ± 13.8 vs 40.6 mmHg ± 13.2, $P > .05$, respectively). In the LISWT group, pain threshold and tolerance were significantly higher at 3 months after the treatment than at the baseline (69.8 mmHg ± 11.8 vs 22.9 mmHg ± 9.0, $P < .01$ and 87.7 mmHg ± 35.7 vs 43.3 mmHg ± 14.7, respectively, $P < .0001$). For the sham group, threshold and tolerance values did not differ between 3 months and the baseline (34.9 mmHg ± 35.1 vs 22.5 mmHg ± 10.22, $P > .05$ and 53.4 mmHg ± 31.5 vs 40.6 mmHg ± 13.2, $P > .05$, respectively).

Wong-Baker Pain FACES Scale

Baseline Wong-Baker scores did not differ between the LISWT and the sham groups (4.6 ± 0.5 and 4 ± 0.6, respectively, $P = .79$). Wong-Baker scores decreased significantly from baseline to 1 month and 3 months after treatment (4 ± 0.64, 2.9 ± 1.2, and 2.5 ± 1.3, respectively, $P < .05$). No differences in Wong-Baker scores were observed in the sham group between the 3 time points (4.6 ± 0.05, 4.0 ± 1.5, and 4.0 ± 2.2, respectively, $P = .3$).

Female Sexual Function Index

No difference in total FSFI baseline scores were observed between the LISWT and the sham groups (17.9 ± 6.3 and 21.1 ± 5.1, respectively, $P = .18$). Total FSFI increased in the LISWT group, from the baseline to 1 month and 3 months after treatment (17.9 ± 6.3, 20.9 ± 6.2, and 22.5 ± 8, respectively $P < .002$). FSFI scores did not differ in the sham group at the 3 time points (21.1 ± 5.1, 21.9 ± 4.7, 21.1 ± 5.1, respectively, $P = .46$).

At the baseline, 1 month and 3 months after treatment, a relatively moderate correlation was found between VAS and the Wong-Baker score (r+0.60, r = 0.75, r = 0.65, respectively, $P < .001$). Changes from the baseline to 3 months in total FSFI were correlated with both VAS and Wong-Baker scores (r = -0.47 and r = 0.76, respectively, $P < .02$).

Patients' Global Impression of Change Scale

Compared with the sham group, for the treatment group, the first component of the PGIC score was higher at 3 months after treatment (first component rang 0-7; 0 = no change, 7 = A grate deal better) (4 ± 1.9 vs 2.3 ± 1.4, $P < .03$), and the second component was lower (second component rang 0-10; 0 = much better and 10 = much worse) (3.3 ± 1.8 vs 5.5 ± 2.3, $P < .006$). These changes both indicated a beneficial effect of LISWT on pain and sexual function, and as a result, on quality of life. Moderate correlations were also observed of the PGIC scores with pain as assessed by the VAS and the Wong-Baker score (r = -0.74 and r = 0.636, $P < .001$).

Safety

One patient in the LISWT group reported self-limited low abdominal pain; no other side effects were reported.

DISCUSSION

To our knowledge, this is the first study that examined the effect of LISWT on women with PVD. We initially had concerns regarding the applicability of this methodology and the probability that it could be associated with a high degree of discomfort due to the hypersensitivity of the introital area. However, we demonstrated that this therapeutic modality was feasible and safe, and not painful.

We believe we found a new effective treatment for alleviating the most bothersome symptom in PVD, pain during penetration and intercourse. Our interventions resulted in improved sexual

function. For the treatment group, a moderate yet significant correlation was found between the decrease in pain symptoms related to penetration at the vestibule area and improvement in sexual function as per FSFI scoring.

PVD is an exhausting pain syndrome that immensely affects quality of sexual life and consequently impairs overall quality of life. Any syndrome or disease in which pain is the dominant symptom poses challenges regarding its evaluation, research methodologies for its investigation, and especially effective therapeutics.

Owing to the high sensitivity to any tactile pressure on the introitus, our first and main concern was the feasibility of applying the shockwave probe directly on the vulvar area. Therefore, we used the low-intensity shockwave range. We showed that LISWT for PVD is feasible, well tolerated, and with a low rate of side effects. The most commonly proposed etiology for PVD is chronic regional inflammation.[1,5,6] Histopathologic examination of vulvar biopsy reveals a chronic inflammatory infiltrate.[22] The physical forces generated by low-intensity shockwaves affect tissue mechanics and can trigger the release of growth factors and anti-inflammatory factors (eNOS and NF-κB).[14] These factors may induce angiogenesis and tissue regeneration, and thus positively regulate the inflammatory process[23,24] and also lead to pain relief. We suggest that LISWT alleviates pain in PVD by inflammatory regulation.

We found a moderate correlation between decreased pain and improvement in sexual function. Because PVD involves various clinical expressions, a multidisciplinary approach is needed to further improve sexual function, that is, a psychological, sexological, or physiotherapeutic intervention during and after LISWT sessions.

STRENGTHS AND LIMITATIONS

The strengths of this study are the randomized controlled design, the correlated subjective questionnaires and the semi-quantitative methodology. Limitations include the relatively small number of patients in a single center and the low reliability of subjective responses.

CONCLUSION

For women with PVD, LISWT applied at the introitus is a feasible, safe, and effective treatment option that may have a beneficial effect on pain relief and sexual function. Although this is a pioneer study on a relatively small number of women, we were impressed by the clinical improvement observed. If similar results will be repeated in larger-scale studies, LISWT should be considered an additional treatment option for PVD in the future. The promising results of this pioneer study suggest the need for further large-scale RCTs to examine the true effect of this treatment modality.

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STATEMENT OF AUTHORSHIP

Conceptualization was contributed by L.L and I.G.; Methodology was contributed by L.L and I.G; Investigation was done by L.L and I.G; Data curation was carriedout by A.G and I.G; Writing—original draft—was performed by O.G; Writing—review and editing—was performed by L.L and I.G; Resources were contributed by L.L and I.G.; Supervision was carried out by L.L and I.G.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jsxm.2020.11.006.