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Extracorporeal Shock Wave Therapy for Treatment of Vulvodynia: A prospective, randomized, double-blind, placebo-controlled study

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Disclosure Statement

All authors declare none conflicts of interest.

Ethics Statement

All procedures performed in the study were in accordance with ethical standards and in an agreement with the 1964 Helsinki Declaration and its later amendments.

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Abbreviations: ESWT= extracorporeal shock wave therapy, VAS= visual analogue scale, CPPS= chronic pelvic pain syndrome, CST= cotton-swab test

Abstract

Background: Currently, there are no effective therapy strategies for idiopathic, non-organic vulvodynia in women. ESWT (extracorporeal shock wave therapy) is a nonsurgical/noninvasive technique widely used to treat musculoskeletal diseases, muscle spasticity and hypertonia, renal and biliary calculi and urological disorders.

Aim: We examined the effects of ESWT on vulvodynia in women.

Study design: A prospective, randomized, double-blind, placebo-controlled study was conducted between 2015 and 2018 following a feasibility study.

Methods: The study included 62 women with vulvodynia for at least 3 months. The women were randomly assigned to either a treatment group (n=31) or a placebo group (n=31).

The patients in the treatment group received perineally applied ESWT weekly (3000 pulses each for four consecutive weeks). The energy flux density was 0.25mJ/mm^2, frequency 4 Hz, focus zone 0-30 mm, therapeutic efficacy 0-90mm, stand-off II. The device used was a standard electromagnetic shock wave unit with a focused shock wave handpiece. The position of the shock wave transducer was changed six times after every 500 pulses. Patients in the placebo group underwent the same treatment procedure, but the handpiece was provided with a placebo stand-off that disabled energy transmission. Subjective pain was self-evaluated by each patient using two tools before and after treatment: a 10 cm linear visual analogue scale (VAS, 0-10) and a cotton-swab test (CST, Goetsch scale 0-4). Follow-ups were done 1, 4, and 12 weeks post-ESWT.

Results: In all, 61 women completed the study. We tested for differences in the VAS and CST within and between the treatment and placebo groups. The testing was between before treatment and particular follow-up. We found significant changes in the treatment group. Reductions in VAS ($p<0.01$) and CST ($p<0.01$) were observed at all three follow-ups. At all assessments, pain reduction was always >30%. In the placebo group there were no statistically significant changes between before and after treatment. There were no differences between the treatment and placebo groups before treatment but statistically significant differences at all three follow-ups (VAS $p<0.01$); CST $p<0.01$). ***Conclusions:*** ESWT seems to reduce pain perception in our treatment group. Thus, we are encouraged to explore this technique further. The method is easily replicable, inexpensive, and without known side effects.

Introduction

Chronic pelvic pain syndrome (CPPS) in women is now recognized as a fairly common condition.[1-6] Several subgroups of CPPS in women have been identified, with vulvodynia being the most frequently occurring disorder of the subgroups.[7,8] A population-based study funded by the National Institutes of Health (NIH) revealed that 15.7% of women reported lower genital tract discomfort persisting ≥3 months. In other studies prevalence rate ranging from 9-12% have been reported.[4,9-12] In 2015, the International Society for the Study of Vulvovaginal Disease (ISSVD, the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS) adopted a new vulvar pain and vulvodynia terminology and classification system that is based on evidence-based information about the disease. It enumerates on the types of pelvic pain connected with many organic diseases and accepts the condition of idiopathic vulvodynia, without any organic reason.[13]

This type of Vulvodynia is a chronic pain syndrome that affects the vulvar area. Symptoms, which have multiple causes, typically include chronic pain, burning, rawness, soreness or irritation in the vaginal area in the absence of an identifiable cause. Myofascial pain, pelvic hypertonia, and trigger points are other conditions discussed as well.[2,7,14] Standard therapy consists of treating neuropathic pain (e.g., with analgesics or neuroactive agents). Additional therapies include pelvic floor rehabilitation combined with surface electromyography, interferon alfa, estrogen creams and botulinum toxin A.[15,16] If conservative treatment is not effective, surgery can be recommended, which is mainly surgical denervation of the vulva. The blockade of trigger points with local anesthetic is also performed.[11,17-21] Most authors seem to advocate a therapy-based approach . Many patients are routinely treated as if they had an infection, even though no infection has been identified or confirmed. Only rarely can complete relief from patient complaints be achieved.[22] The fundamental problem in patients is the long-lasting pain that severely affects their quality of life (QoL).[23] Thus, our aim was to find a simple, safe, modern and promising pain-killing option that could be used to attenuate the pain caused by vulvodynia. ESWT (extracorporeal shock wave therapy) is a novel, nonsurgical and noninvasive procedure that appears to be a viable treatment option for some physical disorders. The use of extracorporeally generated electromagnetic, electrohydraulic, or piezoelectric shock waves for the treatment of calculi in the kidneys or other parts of the urinary tract has radically changed the way these disorders are treated.[24,25] A weaker energy source of ESWT has been used in the

orthopaedic field to treat degenerative and painful joint disorders, plantar fasciitis and muscle disorders.[26] Good results have also been achieved in fracture healings, injuries, and poorly healing wounds.[27,28] Treatment of muscle spasticity and hypertonia in apoplectic patients with ESWT is a topic of interest as well.[29,30] Good results have particularly been achieved in the treatment of pain.[24] Treatments of Peyronie's disease, erectile dysfunction and chronic abacterial prostatitis is not rare nowadays.[31] ESWT for the treatment of CPPS in men has been applied in several studies in the past years.[24,32] These good results and our previous feasibility study [33] suggest ESWT could be a promising treatment of pelvic disorders in women. The ideal aim would naturally be the complete relief of pain in our patients. However, even a clinically relevant pain reduction would be an acceptable accomplishment. The purpose of this study is therefore to determine whether ESWT is effective and safe treatment for idiopathic vulvodynia.

Material and Methods

Study design

The present study was a prospective, randomized, double-blind, placebo-controlled study conducted between 2015 and 2018 following a previous feasibility study[33]. The patients from the feasibility study are not included in this paper. Protocol of the study was approved by the Ethical Committee of the teaching hospital at Charles University Prague. All patients gave their informed consents and confirmed their participation by signing a consent form. The patients were recruited through departments described in 1, 3, in the author's list. The principles of treatment, application and evaluation were done by persons described in the author's list.

Participants

Sixty-two women, aged 24-57 years with objective vulvodynia, defined as vulvar pain of at least 3 months duration during the past 6 months, participated in the study (Fig.1).

Fig.1

Inclusion criteria

Inclusion criteria were based on completing all criteria of vulvodynia:

vulvar vestibulitis syndrome, vestibule-restricted burning/pain elicited by touch or

essential (dysesthetic) vulvodynia burning/pain not only limited to the vestibule and

a positive cotton-swab result (CST, score >0);

vulvodynia persisting for >3 months, defined as experiencing pain on a daily basis;

age 20-75 years;

signing the written consent form;

patient benefits were unobtainable by other therapeutic approaches.

Exclusion criteria

Exclusion criteria were acute pelvic inflammation during the past 6 months;

oncological disease within the past 5 years;

clinically significant haematological disease such as haemophilia or other bleeding disorders;

myocardial infarction or, cardiac arrhythmia within the past 6 months and any serious

metabolic disorder (e.g. diabetes with organic changes).

Subjective pain was self-reported by the patient during her examination and admission to the study. Generalized vulvar pain and burning were quantified using a 10 cm linear visual analogue scale (VAS), (with 0=no pain and 10=maximum pain). Subjective pain was also assessed by the cotton-swab test using the Goetsch scale (from 0–4), with 0 indicating no pain and 4 severe pain.

Randomization

The participants were randomized to either the treatment group or the placebo group using IBM SPSS 23 statistical software. Data were statistically treated using the IBM SPSS 23 system. The right sample size was calculated by IBM Sample Power 3. For calculation, we used the data from our previous feasibility study.[33] We expected a minimal change in VAS of 11% and a SD of 1.3. We needed at least 56 participants (n=28 in each group).[34] We generated two groups of patients for the treatment. The treatment group included 31 patients aged 24-52 (mean age 40 years) while the placebo group comprised 31 patients 27-57 years of age (mean age 39). There were no significant differences in parity and body mass index between the groups. Both groups were fully comparable.

Method

The patients received perineally applied ESWT weekly (3000 pulses each for four consecutive weeks).

All patients were treated in the supine position. The position of the shock wave transducer was changed after every 500 pulses. Six areas, covering the whole vulva and perineum, were treated (Fig.2). The energy flux density was 0.25 mJ/mm2 , frequency 4 Hz, focus zone 0-30 mm and therapeutic efficiency 0-90 mm, stand-off II.).
The device used was a standard electromagnetic shock wave unit with a focused shock wave handpiece DUOLITH® SD1, Storz Medical, Taegerwilen, Switzerland (Fig.3).
The placebo group underwent the same treatment procedure as the treatment group, but the handpiece was fitted with a placebo stand-off containing shock wave absorbing material, a layer of air and air-filled microspheres , which disabled the energy transmission but enabled generation of the sound and shaking mimicking treatment. Moreover, none of our patients had ESWT before, so the blinding was effective.

Fig.2

Fig.3

Treatment assessment

Pain relief within groups was measured by differences between the VAS and CST before treatment and the level of pain after treatment (before versus follow-ups comparison). Follow-ups were done after 1, 4, and 12 weeks post ESWT. Data between the treatment and placebo groups were compared in between comparing (before and particular follow-ups). During treatment and follow-up, concomitant therapy for vulvodynia was prohibited. According to clinical practice, we assume changes > 30% to be clinically relevant.
The purpose of the blinded investigator was to complete the results before conducting the statistical analysis.

Statistical analysis

Considering the normality of the data, we chose appropriate tests for within and between group analysis.

Results

There were 31 patients in the treatment group, and 30 in the placebo group. One patient in the placebo group attended the first follow-up, but not the remaining two. We therefore excluded this patient from all pairwise comparisons. There were no side effects (e.g., bleeding, hematoma, bruising, blistering) associated with the ESWT.
The data were tested for normality using the descriptive numerical method of skewness and kurtosis. Normality of the variables was also assessed by Shapiro-Wilk and Kolmogorov-Smirnov test statistics. Because the data did not follow a Gaussian distribution, we used the nonparametric Wilcoxon signed-ranks test for paired samples to evaluate the treatment and placebo groups. Using VAS and CST, we performed simple analysis of three pairs before and after treatment for each follow-up. Statistical significance was set to $p<0.05$ (two-sided) for all analyses (p-value adjusted to Bonferroni statistics, adjusted $p=0.017$). To calculate differences between the groups the Mann-Whitney U test for nonparametric samples was performed.

Within-group comparisons

In the treatment group we found large, statistically significant differences between patient reported pain before treatment and the three follow-up periods. The p-value in all the

comparisons for VAS was p<0.01 and for CST p<0.01 (Tab.1). Self-reported pain reduction was always > 30%, which corresponds to a clinically relevant result in accordance with the literature. There was no significant decrease in subjective pain in the placebo groups. This finding, consistent with CPPS studies, could probably be explained by the specificity of this pain.

Tab.1

Between-group comparisons

No difference was observed between the treatment and placebo groups before treatment, although statistically significant differences were noted in all three pairs at follow-up for VAS and CST (p<0.01; p<0.01 (Tab.2).

Tab.2

Discussion

To our knowledge, this is the first randomized controlled study that uses ESWT for the treatment of vulvodynia in women. ESWT inducted hyperstimulation of nociceptors and brain pattern changes may play a vital role in CPPS treatment. Some authors have suggested possible interruption of nerve pulses conduction by ESWT. An autonomous nervous system and the coordination between smooth and cross-striated muscles are thought to be involved in a change in structures during treatment with the shock waves.[35,36] Clinical trials have reported the stimulation of growth factors and the promotion and formation of new blood vessels (angiogenesis).[37] In fact, a number of orthopaedic and urological investigations reported no side effects of treatment.[31,38,39] The high tolerability of ESWT and the ability to apply shock waves without anaesthesia permit evaluation without any risks to the patient.[39] Still, we do see some limitations for starting ESWT in terms of local infection, and skin diseases , although these issues are only perfunctorily described in the literature. We did not see the expected placebo effect, similar to CPPS studies in men. Even knowing that the effect of ESWT treatment is dose-dependent, we did not exceed the 0.25 mJ/mm2 level because of potential pain intolerance caused by ESWT application. Without a doubt, reducing daily pain could greatly enhance QoL and enrich daily activities in patients with vulvodynia.

Strengths of this study are its relative simplicity and reproducibility. A major weakness is that we did not have any objective measurements of pain (e.g., looking at images of brain scans).

Conclusions

ESWT seems to be a safe and effective treatment option for vulvodynia in women. Our study demonstrates the impact on pain perception in our group of treated patients. Because the majority of patients with vulvodynia could not normally exist without painkilling drugs, we believe that this modern, noninvasive option to treat vulvodynia could decrease their exclusive use. ESWT is easily replicable and cost-effective (if the device is already in the medical facility's current product inventory). We believe that further discussion is needed on several parameters, including energy flow and the frequency of ESWT applications, although other aspects of the technique should also be investigated.

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Table 1

Comparisons within the Placebo and Treatment group before and after treatment using the Wilcoxon signed-ranks test

	Placebo		After VS Before	Treatment		After VS Before
Parameter	**Mean**	**SD**	**treatment Sig changes**	**Mean**	**SD**	**treatment Sig changes**
VAS_before treatment	6.17	0.98		6.12	0.92	
VAS_1 week	6.1	0.78	NS	2.67	0.71	p<0.01
VAS_4 weeks	6.16	0.92	NS	2.69	0.92	p<0.01
VAS_12_weeks	6.17	0.93	NS	2.63	0.93	p<0.01
CST_before treatment	3.3	0.88		3.3	0.87	
CST_1 week	3.07	0.86	NS	0.7	0.65	p<0.01
CST_4 weeks	3.37	0.76	NS	0.8	0.61	p<0.01
CST_12_weeks	2.97	0.80	NS	0.77	0.62	p<0.01

VAS=visual analogue scale (0-10); CST=cotton-swab test (Goetsch scale, 0-4)

NS=not significant; VS=versus, Sig=significant; SD=standard deviation

Table 2

Comparisons between the Placebo and Treatment group before and after treatment using the the Mann-Whitney U test

Parameter	Placebo group Mean value	Treatment group Mean value	Significancy of changes
VAS_before treatment	6.17	6.12	p=0.93
VAS_1_week	6.1	2.67	p<0.01
VAS_4_week	6.16	2.69	p<0.01
VAS_12_week	6.17	2.63	p<0.01
CST_before treatment	3.3	3.3	p=0.97
CST_1_week	3.07	0.7	p<0.01
CST_4_week	3.37	0.8	p<0.01
CST_12_week	2.97	0.77	p<0.01

VAS=visual analogue scale (0-10); CST=cotton-swab test (Goetsch scale, 0-4)

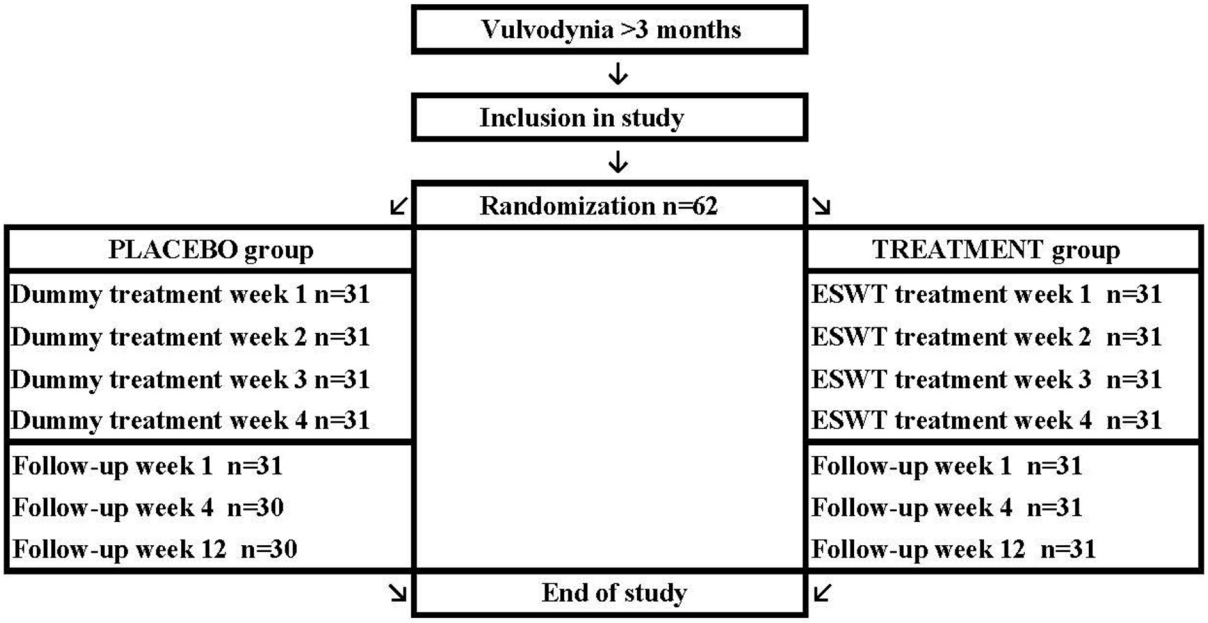

Fig.1 Flow Chart

ESWT=extracorporeal shock wave therapy