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Randomized clinical trial of multimodal physiotherapy treatment compared to overnight lidocaine ointment in women with provoked vestibulodynia: Design and methods

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ABSTRACT

Provoked vestibulodynia (PVD) is a highly prevalent and debilitating condition yet its management relies mainly on non-empirically validated interventions. Among the many causes of PVD, there is growing evidence that pelvic floor muscle (PFM) dysfunctions play an important role in its pathophysiology. Multimodal physiotherapy, which addresses these dysfunctions, is judged by experts to be highly effective and is recommended as a first-line treatment. However, the effectiveness of this promising intervention has been evaluated through only two small uncontrolled trials. The proposed bi-center, single-blind, parallel group, randomized controlled trial (RCT) aims to evaluate the efficacy of multimodal physiotherapy and compare it to a frequently used first-line treatment, topical overnight application of lidocaine, in women with PVD. A total of 212 women diagnosed with PVD according to a standardized protocol were eligible for the study and were randomly assigned to either multimodal physiotherapy or lidocaine treatment for 10 weeks. The primary outcome measure is pain during intercourse (assessed with a numerical rating scale). Secondary measures include sexual function, pain quality, psychological factors (including pain catastrophizing, anxiety, depression and fear of pain), PFM morphology and function, and patients' global impression of change. Assessments are made at baseline, post-treatment and at the 6-month follow-up. This manuscript presents and discusses the rationale, design and methodology of the first RCT investigating physiotherapy in comparison to a commonly prescribed first-line treatment, overnight topical lidocaine, for women with PVD.

1. Introduction

Vulvodynia, a highly neglected chronic pain condition, has a 7–8% prevalence [1]. Considered as the leading cause of pre-menopausal vulvodynia, provoked vestibulodynia (PVD) is characterized by an acute pain at the entry of the vagina during application of pressure or attempted vaginal penetration [2]. PVD is reported to disrupt personal lives, severely affect sexual function and negatively impact quality of life [3,4]. It is also related to relationship problems and psychological distress [5]. Poorly understood, often misdiagnosed or ignored, such pain leads to a high personal cost for patients and substantial financial cost for society. Women multiply their medical visits hoping to find relief and rely mainly on non-evidence-based, ineffective interventions [6].

The exact etiology of PVD remains unclear. Proposed biomedical factors include vaginal infections [7], genetic or immune factors [8], hormonal factors [9], or the proliferation of nociceptors and sensitization [10]. Pelvic floor muscle (PFM) dysfunctions may also play an important role [11–13]. It has been reported that women with PVD have heightened PFM tone as well as inferior PFM strength, coordination

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and endurance compared to asymptomatic women [11–13]. Targeting these dysfunctions, multimodal physiotherapy treatment includes education, biofeedback, manual and insertion techniques [14]. This intervention is judged highly effective by vulvodynia specialists [15] and is listed as a first-line treatment for vulvodynia in clinical guidelines [16,17]. Individual physiotherapy modalities have been shown to reduce pain significantly in women with PVD [18–20]. A randomized controlled trial (RCT) showed a 35% pain reduction during intercourse following PFM biofeedback [18]. Manual therapy and auto-insertion techniques also appear to reduce pain [19,20]. However, it should be emphasized that these isolated modalities do not realistically represent physiotherapy in a clinical setting as described by Hartmann et al. [14] and may yield only partial efficacy compared to a multimodal physiotherapy. To date, the efficacy of multimodal physiotherapy has not been evaluated in a RCT. Only three case reports in women with dyspareunia [21–23] and two small uncontrolled studies [24,25] have investigated the effectiveness of combined treatment. One retrospective study involving 35 women with PVD and one prospective uncontrolled trial in 13 women showed an overall reduction of pain in 71–77% of women, which exceeds the reported effectiveness of the modalities taken separately. Improvements in sexual function and psychological variables are also reported [24,25]. It is therefore important and timely to evaluate the efficacy of the promising multimodal physiotherapy treatment, reflecting current clinical practice, in a RCT design.

Recommended as a first-line treatment in clinical guidelines, topical lidocaine was found to be one of the most commonly prescribed treatments for vulvodynia [15–17]. The hypothesized mechanism of action is that repeated application of this anesthetic could act on nociceptor proliferation and sensitization [10]. Reducing their hyperexcitability is presumed to yield long-lasting pain reduction [10,26]. In a prospective uncontrolled study, Zolnoun et al. [26] showed that overnight use of 5% lidocaine ointment applied for eight weeks significantly reduced pain and improved sexual function in 59% of participants with PVD. Other studies using lidocaine showed improvement in pain and sexual function. However, when comparing lidocaine to other treatments, its efficacy was found nonsignificantly different than biofeedback in the study of Danielsson et al. [27] and desipramine and/or placebo in the study of Foster et al. [28]. The latter's posology and technique of application differed from those of Zolnoun et al. [26], which may explain the lower efficacy. In fact, Danielsson et al. [27] instructed women to apply lidocaine 2% and 5% five to seven times per day while Foster et al. [28] recommended four–five daily applications of lidocaine 2% or 5% diluted in hydrating cream. Overnight lidocaine 5% may represent a better treatment option but its efficacy has never been investigated using a rigorous RCT design.

We designed a bi-center RCT to gather convincing evidence about a recommended intervention (multimodal physiotherapy) and compare it to another frequently used first-line intervention (overnight lidocaine). This paper discusses the rationale, design and methodology as well as challenges encountered during study implementation.

2. Methods

2.1. Design overview

This study consists of a single-blind, parallel-group RCT conducted at two Canadian university hospital centers. The overall design is shown in Fig. 1. The primary aim is to compare the efficacy of multimodal PFM physiotherapy to overnight topical lidocaine for reducing pain during sexual intercourse in women with PVD. Considering the reported effectiveness of the two treatments [24–26] and the opinion of experts, the main hypothesis is that, in comparison to lidocaine, women having physiotherapy will show a greater reduction of pain (post-treatment and at 6-month follow-up compared to baseline assessment). Secondary aims include comparing the effects of the two treatments on: 1) pain quality (affective, sensory and evaluative components); 2) sexual function; 3) psychological variables (catastrophizing, anxiety, depression, fear of pain); 4) PFM morphology and function and 5) patients' global impression of change.

2.2. Participants

A total of 212 nulliparous women with PVD, 18 to 45 years old, were recruited for this study. To be included, women had to report pain in the vestibule area at an average intensity of 5 or more on the Numerical Rating Scale (NRS) during penetration, which is indicative of moderate to severe pain [29]. Both primary (i.e. pain appeared at the first sexual intercourse) and secondary (i.e. pain occurred after successful unpainful intercourse) subtypes were included in the study. In order to confirm the PVD diagnosis, all women underwent a medical history interview and a physical examination including a standardized pelvic examination performed by a gynecologist of our team [18]. This evaluation followed the diagnostic criteria defined by Friedrich [2] and more recently modified by Bergeron et al. [30]: 1) pain in the vestibule following touch or an attempted vaginal penetration; 2) acute pain during the cotton-swab test which consists in applying pressure following a random order to the vulvar vestibule. The inter-rater reliability of this diagnostic method has been demonstrated [30]. Vulvar pain occurring in the absence of an underlying recognizable disease and provoked spontaneously as a result of physical contact can be classified as PVD [31]. Therefore, our assessment procedure aimed to rule out any other specific neuropathology, atrophic vaginitis, dermatoses such as lichen sclerosus, or pathogens such as culture- or smear-proven Candida species, Gardnerella, Trichomonas, herpes simplex, gonorrhea and chlamydia. More details about the inclusion and exclusion criteria are presented in Table 1.

2.3. Baseline assessment

Interested women were invited to contact the research coordinator for a detailed explanation of the study followed by a pre-screening of the eligibility criteria. Participants then took part in a medical examination with a gynecologist of our team to confirm the diagnosis of PVD. Women were then convened to the first evaluation performed by a trained physiotherapist. After signing the informed consent, the women underwent a standardized examination: 1) a structured interview for gathering socio-demographic information, pain, medical and gynecological history; 2) validated questionnaires for evaluating pain, sexual function and psychological variables and 3) physical examination (including PFM morphometry and function). An assessment schedule is shown in Table 2.

2.4. Randomization and blinding

Eligible participants were assigned with equal probability to one of the two treatment groups. Participant randomization was stratified by center, using random permuted blocks of 4 and 6 using a list computer-generated managed by an independent individual. Investigators, data analysts, gynecologists and physiotherapists in charge of the outcome evaluations remain blinded to the trial group allocation. The treatment was explained by the research coordinator at each site after the baseline evaluation and patients were reminded not to reveal their treatment in the initial consent form as well as at the beginning of each evaluation.

2.5. Post-treatment and follow-up assessments

Post-treatment evaluation occurs two weeks after treatment as well as at 6-months follow-up, when the same procedures as in the baseline evaluation are repeated. Further, the participants are asked to rate the perceived improvement and to report any adverse effects related to treatment.