Multimodal physical therapy versus topical lidocaine for provoked vestibulodynia: a prospective, multicentre, randomized trial

Ms. Mélanie Morin, PT, PhD, Ms. Chantale Dumoulin, PT, PhD, Ms, Sophie Bergeron, PhD, Ms. Marie-Hélène Mayrand, MD, PhD, Mr. Samir Khalifé, MD, Mr. Guy Waddell, MD, Ms. Marie-France Dubois, PhD, For the PVD Study Group

PII: S0002-9378(20)30866-8

DOI: https://doi.org/10.1016/j.ajog.2020.08.038

Reference: YMOB 13436

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 25 April 2020

Revised Date: 19 July 2020

Accepted Date: 13 August 2020

Please cite this article as: Morin M, Dumoulin C, Bergeron S, Mayrand M-H, Khalifé S, Waddell G, Dubois M-F, For the PVD Study Group, Multimodal physical therapy versus topical lidocaine for provoked vestibulodynia: a prospective, multicentre, randomized trial, *American Journal of Obstetrics and Gynecology* (2020), doi: https://doi.org/10.1016/j.ajog.2020.08.038.

TITLE PAGE

1) Title

Multimodal physical therapy versus topical lidocaine for provoked vestibulodynia: a prospective, multicentre, randomized trial

2) List of authors

1. Ms. Mélanie MORIN, PT, PhD. School of Rehabilitation, Faculty of Medicine and Health Sciences, Université de Sherbrooke and Research Center of the Centre hospitalier de l'Université de Sherbrooke (CHUS), Sherbrooke, QC (Canada), melanie.m.morin@usherbrooke.ca

2. Ms. Chantale DUMOULIN, PT, PhD, School of Rehabilitation, Faculty of Medicine, Université de Montréal and Research Center of the Institut universitaire de gériatrie de Montréal, Montréal, QC (Canada), chantal.dumoulin@umontreal.ca

3. Ms. Sophie BERGERON, PhD, Department of Psychology, University de Montréal, Montréal, QC (Canada), sophie.bergeron.2@umontreal.ca

4. Ms. Marie-Hélène MAYRAND, MD, PhD, Departments of Obstetrics and Gynecology and Social and Preventive Medicine, Université de Montréal and Research Center of the Centre hospitalier de l'Université de Montréal, Montréal, QC (Canada), mhmayrand@gmail.com

5. Mr. Samir KHALIFÉ, MD, Jewish General Hospital and Royal Victoria Hospital, McGill University Health Center, Montréal, QC (Canada), skhalife@yahoo.com

6. Mr. Guy WADDELL, MD, Department of Obstetrics and Gynecology, CHUS and Université de Sherbrooke, Sherbrooke, QC (Canada), Guy.Waddell@USherbrooke.ca.

7. Ms. Marie-France DUBOIS, PhD, Department of Community Health Sciences, Faculty of Medicine and Health Sciences, Université de Sherbrooke and Research Center on Aging, Sherbrooke, QC (Canada), Marie-France.Dubois@USherbrooke.ca.

8. For the PVD Study Group*

*The PVD Study Group includes the following authors and clinical collaborators: Dr. Isabelle Girard and Dr. Yves-André Bureau from the Université de Sherbrooke and the Centre hospitalier de l'Université de Sherbrooke as well as Dr. Stéphane Ouellet, Dr. Barbara Reichetzer, Dr. Laurence Simard-Émond and Dr. Ian Brochu from Université de Montréal Centre hospitalier de l'Université de Montréal.

3) Disclosure statement of any potential of interest

The authors report no conflict of interest.

4) Financial support for the research

This study was supported by the Canadian Institutes of Health Research (MOP-115028). Drs Morin and Mayrand received salary awards from the Fonds de la recherche du Québec – Santé. Dr. Dumoulin received salary award from the Canadian Research Chair Tier II program. The laboratory infrastructures were funded by the Canadian Foundation for Innovation. The study funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

5) Clinical trial identification number and URL of registration site

Date of registration: October 19th, 2011

Date of initial participant enrollment: May 11th, 2012

ClinicalTrials.gov Identifier NCT01455350; https://clinicaltrials.gov/ct2/show/NCT01455350

6) Paper presentation information

M. Morin, C. Dumoulin, S. Bergeron, M-H. Mayrand, S. Khalifé, G. Waddell, M-F. Dubois, PVD Group. A randomized clinical trial evaluating the efficacy of multimodal physical therapy in comparison to overnight topical lidocaine in women with provoked vestibulodynia. 3rd World Congress of Abdominal and Pelvic Pain International Pelvic Pain Society (IPPS), Washington, USA, October 11-15, 2017. *****Top rated abstract*****

7) Disclaimer

N/A

8) Corresponding author's contact information

Mélanie Morin, PT, Ph.D.

School of Rehabilitation, Faculty of Medicine and Health Sciences,

University of Sherbrooke

3001, 12th Avenue Nord

Sherbrooke (Québec)

Canada J1H 5N4

Telephone number: 819-346-1110, extension 13818

E-mail: Melanie.M.Morin@usherbrooke.ca

WORD COUNT

Abstract: 409 words/250-500

Main text: 3343 words/3000

CONDENSATION, SHORT TITLE, AJOG AT A GLANCE, AND KEYWORDS

CONDENSATION: Physical therapy is effective for reducing pain and sexual distress as well as improving sexual function in women with provoked vestibulodynia compared to topical lidocaine.

SHORT TITLE: Efficacy of physical therapy versus lidocaine for provoked vestibulodynia

AJOG AT A GLANCE

A. Why was the study conducted?

This study was conducted to determine the efficacy of multimodal physical therapy in women with provoked vestibulodynia in comparison with topical lidocaine, a frequently prescribed first-line medical intervention.

B. What are the key findings?

Multimodal physical therapy showed both statistically significant and clinically meaningful improvements post-treatment compared to overnight topical lidocaine for pain intensity and all secondary outcomes (pain quality, sexual function, sexual distress, satisfaction and participants' impression of change). All benefits of physical therapy were maintained at 6-month follow-up.

C. What does this study add to what is already known?

Findings from this study confirm that multimodal physical therapy is effective for provoked vestibulodynia and thereby, provide robust evidence for recommending physical therapy as the preferred first-line treatment.

KEYWORDS: Chronic pelvic pain, biofeedback, manual therapy, pain education, pelvic floor, physiotherapy, psychological distress, randomized clinical trial, rehabilitation, sexual dysfunction, vulvodynia, women's health

ABSTRACT

BACKGROUND: Provoked vestibulodynia is the most common subtype of chronic vulvar pain. This highly prevalent and debilitating condition is characterized by acute recurrent pain located at the entry of the vagina in response to pressure application or attempted vaginal penetration. Physical therapy is advocated as a first-line treatment for provoked vestibulodynia but evidence supporting its efficacy is scarce.

OBJECTIVE: The purpose of this study was to establish the efficacy of multimodal physical therapy compared to topical lidocaine, a frequently used first-line treatment.

STUDY DESIGN: We conducted a prospective, multicentre, parallel group, randomized clinical trial in women diagnosed with provoked vestibulodynia recruited from the community and four Canadian university hospitals. Women were randomly assigned (1:1) to receive either weekly sessions of physical therapy or overnight topical lidocaine (5% ointment) for 10 weeks. Randomization was stratified by center using random permuted blocks from a computer-generated list managed by an independent individual. Physical therapy entailed education, pelvic floor muscle exercises with biofeedback, manual therapy and dilation. Assessments were conducted at baseline, post-treatment and 6-month follow-up. Outcome assessors, investigators and data analysts were masked to allocation. The primary outcome was pain intensity during intercourse evaluated with the numerical rating scale (NRS 0-10). Secondary outcomes included pain quality (McGill-Melzack pain questionnaire), sexual function (Female Sexual Function Index), sexual distress (Female Sexual Distress Scale), satisfaction (NRS 0-10) and participants' impression of change (The Patient's Global Impression of Change). Intention-to-treat analyses were conducted using piecewise linear-growth models.

RESULTS: Among 212 women recruited and randomized, 201 (95%) completed the post-treatment assessment and 195 (92%) the 6-month follow-up. Multimodal physical therapy was more effective than lidocaine for reducing pain intensity during intercourse (between groups pre-post slope difference P<0.001; mean group post difference 1.8; 95% confidence interval (CI) 1.2 to 2.3) and results were maintained at 6-month follow-up (mean group difference 1.8, 95%CI 1.2 to 2.5). The physical therapy group also performed better than the lidocaine group in all secondary outcomes (pain quality, sexual function, sexual distress, satisfaction and participants' impression of change) at post-treatment and 6-month follow-up. Moreover, the changes observed following physical therapy were shown to be clinically meaningful. Regarding participants' impression of change, 79% of women in the physical therapy group reported being very much or much improved compared to 39% in the lidocaine group (p<0.001).

CONCLUSION: Findings provide strong evidence that physical therapy is effective for pain, sexual function and sexual distress, and support its recommendation as the first-line treatment of choice for provoked vestibulodynia.

MAIN TEXT

INTRODUCTION

Vulvodynia or chronic vulvar pain has a prevalence rate as high as 7-18%.[1,2] Although vulvodynia is as frequent as other well-known chronic pain conditions such as low back pain, arthrosis or fibromyalgia,[3] it remains poorly understood, often misdiagnosed or even ignored by health professionals.[4] Vulvodynia leads to high psychological distress, significant disruption in all aspects of sexual function, and altered quality of life.[5] Additionally, vulvodynia carries an annual economic burden of $31-72 billion in the US.[6] The principal subtype of vulvodynia, provoked vestibulodynia, is characterized by pain upon pressure at the vulvar vestibule or attempted vaginal penetration.[7] Women multiply their medical visits in hopes of finding relief and are confronted with limited effective treatment options.[4] Indeed, well-designed randomized trials have thus far failed to prove the efficacy of first-line medical treatments for reducing pain in women with provoked vestibulodynia (e.g. gabapentin, tricyclic antidepressant, botulium toxin).[8-10]

Physical therapy, usually consisting of biofeedback, pelvic floor muscle exercises, manual therapy, dilation and education,[11] may potentially fill this therapeutic void and is perceived as the most effective intervention according to medical experts.[12] However, the efficacy of physical therapy is supported only by small uncontrolled or pilot studies showing significant reductions in pain and improvements in sexual function.[13-16] As stated in a recent systematic review,[17] reliable evidence based on randomized trials is needed to confirm these promising findings. Topical lidocaine is currently the most frequently prescribed first-line intervention.[12] In Zolnoun et al.'s single-arm prospective study,[18] overnight 5% lidocaine ointment significantly reduced pain and improved sexual function. This application and dose appear

more effective than other available applications (e.g. repeated daily application, 2% or 5% lidocaine diluted in hydrating cream) as they were shown non-effective in two randomized trials.[9,19] We therefore conducted a randomized clinical trial to determine the efficacy of physical therapy in women with provoked vestibulodynia compared to overnight topical lidocaine.

MATERIALS AND METHODS

Study Design

In this randomized, parallel-group, multicenter, clinical trial, physical therapy was compared to a frequently prescribed first line medical treatment, topical lidocaine. Ethics approval for the trial was granted by the Research Ethics Board of the two directing sites (Sherbrooke and Montreal, Qc, Canada) and participating hospitals. The study was registered in ClinicalTrials.gov (NCT01455350) and details of the study protocol were published previously.[20]

Participants

Participants were recruited between May 2012 and August 2015 by means of posters in universities; medical clinics and stores; web initiatives; referrals by health professionals; newspaper ads; and public conferences. Nulliparous women, aged 18-45, were included if they reported pain during sexual intercourse for >6 months with an averaged intensity of ≥5/10 on a numerical rating scale (NRS). Women also had their diagnosis of provoked vestibulodynia confirmed by the study gynecologists according to current recommendations (e.g differential diagnosis including infections were ruled out and a positive cotton swab test was obtained).[20] The main exclusion criteria were: 1) other urogynecological and vulvar pain

conditions (e.g. unprovoked pain, deep dyspareunia); 2) having previously received physical therapy or overnight lidocaine; 3) any coexisting significant medical conditions likely to interfere with the study procedures. More details on eligibility criteria are available elsewhere.[20]

Randomization and masking

Women who met the eligibility criteria after a phone screening interview and a gynaecological assessment underwent a baseline assessment. Participants were then randomized 1:1 to physical therapy or lidocaine for ten weeks. Randomization was stratified by center using random permuted blocks (size 4-6) from a computer-generated list designed by an independent statistician. This concealed randomization list was thereafter managed by an independent individual who assigned participants. Investigators, data analysts, gynaecologists and outcome evaluators (trained physical therapist not involved in treatments) remained blinded to group allocation.

Interventions

Physical therapy treatment consisted of ten weeks of individual one-hour sessions (Appendix 1). The physical therapists providing treatments were all certified physical therapists with postgraduate qualifications in women's health including courses in pelvic pain. They had all received a standardized training for the treatment protocol and had access to mentoring and supervision when needed. The modalities composing the standardized physical therapy treatment protocol were selected to reflect current clinical practice.[11] As an important component of physical therapy, the educational program included various topics such chronic pain management, muscle pathophysiology and sexual functioning. Manual

therapy techniques, applied for 20-25 minutes, were adapted to each participant's condition (e.g. the amount of pressure varied according to tolerance) and evolved throughout the sessions. They consisted of vulvar desensitization, pelvic floor muscle stretching, myofascial release, conjunctive tissue manipulation, and neuromuscular re-education. Similar techniques were also applied to the hip and abdominal muscles. The pelvic floor muscle exercises assisted by biofeedback were practiced for 20 minutes to improve muscle relaxation and function. The home exercise program incorporated pelvic floor contractions (5x/week) as well as stretching exercises using a dilator and vestibule tissue mobilization (3x/week).

The overnight topical lidocaine treatment was based on the application protocol described by Zolnoun et al.[18] Participants were asked to apply a copious amount of lidocaine 5% ointment (50mg/g, Lidocan®, Odan Lab, 35g) on the vestibule area at bedtime. They also had to place a small gauze containing ointment (the size of a marble) at the vestibule area and maintain continuous contact through the night for ≥8 hours. In addition to written instructions, the research coordinator carefully explained the procedure to each participant and followed-up with weekly phone calls.

Study outcomes

Participants were convened to an assessment session conducted by a trained physical therapist blinded to group assignation at baseline, post-treatment and at 6-month follow-up. The primary outcome was the average pain intensity during intercourse on an NRS (from 0, no pain, to 10, the worst possible pain) measured at baseline, post-treatment and 6-month follow-up. Recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[21] and a vulvodynia outcome consensus group,[22] this scale has

been widely used in clinical trials for vulvodynia and other chronic pain conditions and has shown excellent psychometric properties.[17,21] The pain intensity rating can be categorized as mild (1-4), moderate (5-6) or severe (7-10),[23] a reduction of 1.5 or 30% is indicative of a minimal clinically important difference (MCID).[21]

Secondary outcomes were measured with validated self-administered questionnaires at the three time points. Pain quality including its sensory, affective and evaluative components was assessed with the McGill-Melzack pain questionnaire (MPQ).[24] The Female Sexual Function Index (FSFI) was used as a multidimensional measure of sexual function, which encompasses desire, arousal, lubrication, orgasm and satisfaction.[25] Sexually-related distress was evaluated with the Female Sexual Distress Scale (FSDS).[26] Additional secondary outcomes pertaining to treatment effects on psychological variables and pelvic floor muscle morphology and function were collected and will be presented in further publications.

Satisfaction with treatment was evaluated at post-treatment and at 6-month follow-up by one question (from 0, completely dissatisfied, to 10, completely satisfied). The Patient's Global Impression of Change (PGIC) was employed to evaluate perceived reduction in pain using a 7-point scale.[21] Treatment adherence was evaluated by means of a participant daily diary which was reviewed weekly by the treating physical therapist or, for women in the lidocaine group, by the research coordinator during weekly phone call. The percentage of exercises completed or ointment applied were considered. Participants were also asked to report any side effects and the use of any other treatment throughout their participation in the study.

Statistical analyses

The total sample size estimate of 212 was based on the primary outcome of pain during sexual intercourse using the NRS. Statistical power analysis examined the requirements to detect the most conservative MCID of 1.5 points between the two treatments (two-sided α=0.05, power=0.80, 3.47 standard deviation[18]) and an expected dropout of 20% (further justification available elsewhere[20]). Intention-to-treat analyses were conducted to evaluate the efficacy of the two interventions using a multilevel model of change adjusted for the directing sites.[27] Multilevel models of change (using SAS PROC MIXED) were used as proposed by Singer & Willett.[27] The primary outcome and continuous secondary outcomes were analyzed in relation to values at the different time-points, slopes between time points and differences in slopes between treatments. This type of analysis was selected because it takes into account the dependency between repeated measures without requiring identical intervals between time-points.[27] A piecewise linear-growth model was estimated as we anticipated the slope between baseline and post-treatment evaluations being steeper than that at 6-month follow-up. Time was considered as an independent variable and treatment outcomes as dependent variables.

As for the treatment group, site was entered in the model as a fixed factor as no clustering effect was expected. Missing data were few (less than 8%) and multilevel models allowed us to use partial data from women who did not participate in all measurements. No additional treatment of missing data was therefore undertaken since it has been suggested that it is not necessary with less than 10% of missing data[28] and multiple imputations should not be used with longitudinal data analyzed with mixed-effects models.[29,30] Chi-square tests were used to compare the two groups for the proportion of participants presenting meaningful clinical changes and for outcomes pertaining to the participant's impression of change. The number

needed to treat (NNT) was computed with is 95% confidence interval (CI) to help translate the dichotomous findings into clinically useful counseling points. Statistical analyses were performed with SAS 9.4 (SAS Institute) and SPSS 24 (IBM software) at the 5% level (two-sided).

RESULTS

Participants

Of the 537 women interested in participating, 212 were found eligible and randomized to either physical therapy (105) or lidocaine (107) (Figure 1). As shown in Table 1, baseline characteristics were similar between the two groups. Moreover, there were no significant differences in baseline characteristics and outcomes between women who completed the trial and those who did not.

Primary outcome

Mean estimated pain intensity during intercourse over time derived from the multilevel model is presented in Figure 2A. Pain was reduced for women in both the physical therapy and the lidocaine groups from baseline to post-treatment as revealed by statistically significant within-group slopes (both P<.001). However, physical therapy was found to be more effective than lidocaine for reducing pain according to the between-group slope difference (P<.001) and mean estimated difference between groups at post-treatment (1.8; 95%CI: 1.2 to 2.3; P<.001) (Table 2). Results were maintained at 6-month follow-up as indicated by non-significant changes from post-treatment to follow-up (within-group slope for physical therapy P=0.25 and for lidocaine P=.11). Therefore, physical therapy remained more effective than lidocaine for

reducing pain intensity at 6-month follow-up (mean estimated pain difference between treatments 1.8; 95%CI: 1.2 to 2.5; P<.001) (Table 2).

172

173 **Secondary outcomes**

174 Mean estimated scores derived from the multilevel model for pain quality, sexual function and
175 distress over time according to treatment group are illustrated in Figure 2 B-D. Mean
176 estimated differences between groups are presented in Table 2. Women in both groups had
177 positive impacts for all outcomes from baseline to post-treatment, as revealed by statistically
178 significant within-group slopes (all P<.001). However, physical therapy was more effective
179 than lidocaine for pain quality and sexual function and distress according to the difference in
180 group slopes (all P<.001) and mean estimated difference between groups at post-treatment
181 (all P<.001). For all outcomes, benefits were maintained at 6 months as indicated by non-
182 significant changes from post-treatment to follow-up. Therefore, physical therapy remained
183 more effective than lidocaine at 6-month follow-up for all secondary outcomes (all P<.001
184 between group scores).

185

186 As for treatment satisfaction (Table 2), women in the physical therapy group also reported
187 higher satisfaction with treatment compared to women in the lidocaine group at post-
188 treatment and 6-month follow-up (P<.001). As measured by the PGIC at post-treatment, 79%
189 of women in the physical therapy group reported being very much or much improved
190 compared to 39% in the lidocaine group (p<.001).

191

192 **Clinically important changes and meaningful outcomes**

193 Table 3 shows that, considering a MCID of 30% reduction in pain intensity,[21] significantly
194 more participants in the physical therapy group than in the lidocaine group showed
195 improvement: 91% versus 62% at post-treatment, and 89% versus 55% at follow-up (P<.001

derived from chi-square tests). Moreover, significantly more women in the physical therapy group presented no or only mild pain intensity (P<.001). The physical therapy group also met the standards for clinically meaningful improvement in the MPQ significantly more often than did the lidocaine group (Table 3). Higher percentages of women in the physical therapy group were no longer considered at risk of sexual dysfunction or sexual distress according to the clinical cut-off scores (Table 3). Also supporting clinically meaningful outcomes, the NNT obtained for all outcomes were very low, ranging between 2.9 and 5.6 which indicates that only a small number of patients is needed to obtain significant benefit in comparison with lidocaine.

Treatment adherence

Regarding adherence to treatment, with the exception of the six participants who discontinued the intervention, all other women attended all ten of their physical therapy sessions. The overall adherence to home exercises had a median of 85% [Interquartile range 75-91%]. Except for the five participants who discontinued the intervention, all other women completed the ten weeks of lidocaine application. The overall adherence for lidocaine had a median of 91% [Interquartile range 83-96%]. With regard to other treatments while under trial, two women in the physical therapy group had psychotherapy while in the lidocaine group, three had in psychotherapy, four physical therapy and one topical corticosteroids. The results of the primary and secondary outcomes remained unchanged when removing these participants from the analyses.

Adverse events

No adverse events were reported by women in the physical therapy group. In the lidocaine group, one participant discontinued the study because of a dermatitis reaction to lidocaine and 15 (15%) women reported a minor irritating or burning sensation.

DISCUSSION

Principal findings

This randomized clinical trial showed that physical therapy is more effective than lidocaine in reducing pain and sexual distress as well as improving sexual function. The observed benefits in the physical therapy group were sustained at 6-month follow-up and were also clinically significant as they exceeded the specified thresholds for MCID and clinical cut-off for all outcomes.

Results in context

Pain during intercourse significantly declined from baseline to post-treatment and results were sustained at 6-month follow-up, suggesting that both treatments were successful in alleviating pain. However, physical therapy proved to be significantly more effective. This result is consistent with those of previous small non-randomized or pilot studies suggesting significant reduction in pain after physical therapy.[14-16] In a retrospective study by Hartmann and Nelson (n=24)[16] and a prospective uncontrolled study by Goldfinger et al. (n=13)[14], the extent of changes observed appear comparable to the effect demonstrated in our trial with baseline pain at 7-8/10 and post-treatment pain at 2-3/10. Another pilot study by Goldfinger et al[15] also reported significant changes in pain intensity after physical therapy but failed to detect any

243 significant difference with cognitive behavioral therapy. This could be explained by their lack
244 of statistical power as they included only ten women per group. Interestingly, in our study, the
245 benefits of physical therapy were not only statistically significant but also clinically relevant
246 given that 91% and 89% met the standards for clinically meaningful reduction in pain[21] at
247 post-treatment and follow-up, respectively (compared to 52% and 46% for lidocaine). These
248 findings are in line with those of Goldfinger et al.[15] reporting that 90% of participants had
249 reached the clinically significant change in pain after physical therapy. It is also worthwhile
250 noting that most women in our trial had no or only mild pain[23] after physical therapy. In
251 addition to pain intensity, we also showed that pain quality (MPQ) taking into account
252 affective, sensory and evaluative components was reduced after physical therapy and at
253 follow-up compared to lidocaine. This contrasts with Goldfinger et al.'s[15] pilot study indicating
254 changes in only one component of the MPQ at post-treament, which were not sustained at
255 the 6-month follow-up. The greater benefits observed in our study may be explained by a
256 higher number of physical therapy sessions, an exercise program designed according to the
257 latest evidence on pelvic floor alterations in women with vestibulodynia[31] and a more
258 throrough educational program focusing on chronic pain management.
259
260 Sexual dysfunction is, along with pain during intercourse, the main complaint of women with
261 provoked vestibulodynia.[5] Significant improvements in sexual function and sexual distress
262 were observed in both groups but physical therapy was found to be more effective than
263 lidocaine and the results were sustained at the 6-month follow-up. A higher percentage of
264 women were no longer within clinical ranges of sexual dysfunction and distress after physical
265 therapy. These results concur with those of uncontrolled studies suggesting improvement in
266 sexual function after physical therapy.[14,16] Overall, our findings emphasize the importance of

making sexual dysfunction an intervention target that includes a comprehensive psychosexual educational program combined with the use of dilators to help women acheive painfree sexual intercourse.

In terms of participant perceived improvements, women in the physical therapy group were more satisfied and perceived more improvement: 79% of women reported being very much or much improved after treatment compared to 39% in the lidocaine group. This corroborates the results of two previous studies reporting that 72-77% of women had significant improvement.[13,14]

Clinical and research implications

Although the clinical guidelines of leading societies concur to recommend physical therapy as a first-line intervention for provoked vestibulodynia,[32,33] access to treatment remains limited and arduous.[2,6,34] Our findings provide strong evidence that physical therapy is effective in women with provoked vestibulodynia with statistically significant and clinically meaningful benefits sustained at 6-month follow-up. We hope these results will encourage decision makers, administrative stakeholders, insurance companies and clinicians to promote and facilitate access to physical therapy treatments. Further studies are needed to investigate the implementation of physical therapy treatment including facilitators and barriers to treatment access and coverage.

Strengths and weaknesses

The main strengths of this trial were the use of a randomized design, sufficiently powered intent-to-treat analyses, rigorous eligibility criteria with precise diagnosis of provoked

vestibulodynia, long-term follow-up as well as physical therapy treatment being relevant to current practice. The selection of outcomes complies with current guidelines from leading consensus groups[21,22] recommending patient-reported outcomes to capture the multidimensional experience of pain and sexual dysfunctions. Furthermore, participants' adherence to the trial procedures and the intervention was high. This could be explained by the multimodal, intensive and supervised treatment proposed, which has been suggested to favor adherence.[19,35] We also offered a flexible schedule for the participants and employed experimented physical therapists. As for limitations, this study did not include a placebo arm, given that validated and credible sham physical therapy has never been investigated. In this context, the CONSORT extension for behavioral treatment advocates for the use of an active comparator reflecting current practice.[36] Topical lidocaine was thus selected as it corresponds to the common usual care for PVD and we therefore intentionally limited the number of contacts with the health professional to weekly phone calls to reliably represent treatment delivery in clinical settings. Moreover, as highlighted in the CONSORT extension,[36] blinding of participants is nearly impossible to achieve with these types of interventions. It is therefore recommended to minimize bias which we aimed to achieve by using assessors not involved in treatment and blinded to group assignation. It should also be pointed out that the risk of bias is likely low given that similar studies failed to demonstrate the superiority of active treatments (biofeedback[19] and antidepressant[9]) in comparison with lidocaine. Furthermore, nulliparous women aged 18-45 years old were targeted in this study. This age group was shown to be generalizable to the population of women with PVD given that it covers 87% of affected women.[2] Most importantly, it allowed to control for factors confounding the PVD diagnosis such as childbirth-related lesions and genitourinary syndrome of menopause. Likewise, women with other types of chronic vulvar pain (e.g. deep dyspareunia, unprovoked pain,

dermatological conditions) were excluded in order to investigate treatments designed to specifically address PVD. The inclusion of these other types of pain would have required adapting our treatment protocol and would probably have introduced a bias favoring physical therapy treatment as topical lidocaine is not likely to have a significant effect for these conditions. Furthermore, multiple physical therapy modalities were selected for the adequate portrayal of current clinical practice.[11] This contributes to the external validity of our study but prevents us from discussing the isolated contribution of each modality. Given the complexity of vulvar pain conditions, it is unlikely that a single modality could address the multidimensionality of pain. Indeed, the efficacy of our multimodal treatment appears to largely outweigh that of single isolated modalities.[17]

Conclusions

Our findings confirm that physical therapy is effective for reducing pain and sexual distress, as well as for improving sexual function. They thus provide strong evidence for recommending physical therapy as the preferred first-line treatment for provoked vestibulodynia.

ACKNOWLEDGMENTS

This study was supported by the Canadian Institutes of Health Research (MOP-115028). Drs Morin and Mayrand received salary awards from the Fonds de la recherche du Québec – Santé. Dr. Dumoulin received salary award from the Canadian Research Chair Tier II program. The laboratory infrastructures were funded by the Canadian Foundation for Innovation. The authors would also like to extend their gratitude to the study coordinators and data analysts (Marie-Soleil Carroll, Mélanie Morin, Stéphanie Pontbriand-Drolet, Yvonne Ruella, Olivia Dubois and Marie-Pierre Garant), as well as the physical therapy involved in treatments and assessments. We would also like to thank all the study participants for their support and dedication to this research project.

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TABLES

Table 1. Characteristics of the participants at baseline according to treatment group

	Physical therapy (n=105)	Lidocaine (n=107)
Age (years)	22 [21-26]	22 [21-25]
< 20	13 (12%)	10 (9%)
20-25	64 (61%)	74 (69%)
26-30	21 (20%)	17 (16%)
31-35	6 (6%)	5 (5%)
>35	1 (1%)	1 (1%)
Body mass index (kg/m^2)	22 [20-24]	22 [20-24]
Place of birth		
North America	93 (89%)	96 (90%)
Europe	3 (3%)	4 (4%)
Latin/South America	1 (1%)	5 (4%)
Other	8 (7%)	2 (2%)
Income in Canadian $		
0-9 999$	35 (33%)	41 (38%)
10 000-19 999$	33 (32%)	30 (28%)
20 000-39 999$	21 (20%)	17 (16%)
≥40 000-59 999$	16 (15%)	19 (18%)
Education		
High school	22 (21%)	19 (18%)
College	44 (42%)	51 (48%)
University - Graduate	39 (37%)	36 (34%)
Relations status		
Married	7 (7%)	8 (7%)

Civil union (living with a partner for ≥2 years)	33 (31%)	31 (29%)
In relationship	65 (62%)	68 (64%)
Relationship duration (years)	2.7 [1.1-4.1]	2.2 [1.1-4.0]
Pain intensity during intercourse (NRS/10)	7.5 [6.0-8.0]	7.0 [6.0-8.0]
moderate 5-6/10	35 (33%)	29 (27%)
severe 7-10	70 (67%)	78 (73%)
Duration of pain (years)	3.0 [1.6-6.0]	2.5 [1.5-5.5]
≥≤ 0.5 - 1 year	19 (18%)	15 (14%)
> 1 - 5 years	53 (51%)	63 (59%)
> 5 years	33 (31%)	29 (27%)
Type of PVD		
Primary (pain since first sexual intercourse)	42 (40%)	33 (31%)
Secondary (pain acquired after a period of pain-free sexual intercourse)	63 (60%)	74 (69%)
Frequency of intercourse (per month)	3.5 [1.0-8.0]	4.0 [1.0-8.0]
Use of hormonal contraceptive	85 (81%)	85 (79%)
Previous treatment attempted		
Lidocaine prior intercourse	14 (13%)	14 (13%)
Psychotherapy	6 (6%)	5 (5%)
Topical oestrogen	6 (6%)	8 (7%)
Antidepressant	2 (2%)	0 (0%)
Natural product	3 (3%)	4 (4%)

449 Data are median [Interquartile range] or n (%).

450 **Table 2. Study measures at baseline, post-treatment and 6-month follow-up and**
451 **differences between treatment groups.**

	Physical therapy (n=105)	Lidocaine (n=107)	Mean difference between treatment groups (95%CI)	P-values
Pain intensity (NRS)				
Baseline	7.3 (0.2)	7.3 (0.2)	0.0 (-0.4 to 0.5)	.88
Post-treatment	2.7 (0.2)	4.5 (0.2)	1.8 (1.2 to 2.3)	<.001
6-month follow-up	3.0 (0.2)	4.8 (0.2)	1.8 (1.2 to 2.5)	<.001
Pain quality (MPQ)				
Baseline	28.2 (1.3)	30.5 (1.3)	2.3 (-1.3 to 5.9)	.20
Post-treatment	13.7 (1.3)	21.5 (1.3)	7.8 (4.2 to 11.4)	<.001
6-month follow-up	15.0 (1.3)	22.8 (1.3)	7.8 (4.2 to 11.4)	<.001
Sexual function (FSFI)				
Baseline	20.1 (0.8)	20.7 (0.6)	0.5 (-1.2 to 2.2)	.55
Post-treatment	28.0 (0.6)	23.5 (0.6)	-4.4 (-6.1 to -2.7)	<.001
6-month follow-up	27.3 (0.6)	24.0 (0.6)	-3.3 (-5.0 to -1.6)	<.001
Sexually related distress (FSDS)				
Baseline	31.8 (1.1)	30.5 (1.1)	-1.3 (-4.3 to 1.8)	.41
Post-treatment	12.4 (1.1)	19.0 (1.1)	6.5 (3.4 to 9.7)	<.001
6-month follow-up	14.2 (1.2)	19.8 (1.2)	5.6 (2.4 to 8.8)	<.001
Satisfaction (/10)				
Post-treatment	8.9 (0.1)	5.6 (0.3)	3.3 (2.7 to 4.0)	<.001
6-month follow-up	8.5 (0.2)	5.2 (0.3)	3.2 (2.6 to 4.0)	<.001
Participants' perceived improvement (PGIC) [a]				
very much improved	43 (43%)	14 (14%)	-	
much improved	35 (35%)	26 (25%)	-	<.001
minimally improved	20 (20%)	31 (30%)	-	

no change	1 (1%)	29 (28%)	-
minimally worse	0 (0%)	0 (0%)	-
much worse	0 (0%)	2 (2%)	-
very much worse	0 (0%)	0 (0%)	-

Shown are the mean estimated scores and standard error derived from multilevel model according to treatments and mean difference between treatments (95% confidence interval (CI)). Number (and percentages) of participants are presented for perceived improvement. P-values denote between-group differences. Numerical pain rating scale (NRS); McGill-Melzack Pain Questionnaire (MPQ); Female Sexual Function Index (FSFI); Female Sexual Distress Scale (FSDS); Patients' Global Impression of Change (PGIC).

[a] Only post-treatment data are presented because the 6-month assessment was misconceptualized by some participants who reported changes from post-treatment to 6 months instead of the overall effect from baseline to 6 months.

463 **Table 3. Participants with clinically important changes and clinically meaningful**
464 **outcomes**

	Physical therapy	Lidocaine	P-values	Number needed to treat (NNT) (95%CI)
	no. of patients (%)			
Distribution of participant with clinically important changes				
Pain intensity (NRS)[a]				
30% reduction on NRS at post-treatment	90 (91%)	63 (62%)	<.001	3.4 (2.5-5.5)
30% reduction of NRS at 6-month follow-up	84 (89%)	56 (55%)	<.001	2.9 (2.2-4.5)
Pain quality (MPQ) [b]				
30% reduction on MPQ at post-treatment	69 (71%)	53 (52%)	.006	5.6 (3.2-22.4)
30% reduction on MPQ at 6-month follow-up	62 (67%)	45 (46%)	.004	4.7 (2.8-12.9)
Distribution of participant with clinically meaningful outcomes (based on clinical cut-off)				
Pain intensity (NRS) [c]				
Post-treatment				
None/Mild (0-4)	84 (85%)	52 (51%)		
Moderate (5-6)	11 (11%)	27 (26%)	<.001	2.9 (2.2-4.6)[f]
Severe (7-10)	4 (4%)	23 (23%)		
6-month follow-up				
None/Mild (0-4)	73 (78%)	48 (48%)		
Moderate (5-6)	17 (18%)	27 (27%)	<.001	3.3 (2.3-5.8)[f]
Severe (7-10)	4 (4%)	26 (26%)		
Sexual function (FSFI)[d]				
Sexually functional (≥26.55) at post-treatment	65 (66%)	44 (43%)	.001	4.4 (2.8-10.9)
Sexually functional (≥26.55) at 6-month follow-up	59 (63%)	39 (39%)	.001	4.1 (2.6-9.5)
Sexually related distress (FSDS)[e]				

No sexually distress (<15) at post-treatment	65 (66%)	48 (47%)	.008	5.8 (3.1-19.5)
No sexually distress (<15) at 6-month follow-up	56 (60%)	36 (37%)	.002	4.2 (2.7-9.7)

Distribution of participants presenting clinically important changes and/or clinically meaningful outcomes (derived from clinical cut-off score) are presented in agreement with the available literature. P values were calculated with the use of the chi-square tests.

[a] MCID corresponds to a reduction of 30% in pain intensity evaluated with the numerical pain rating scale (NRS).[21]

[b] MCID corresponds to a reduction of 30% on the McGill-Melzack Pain Questionnaire (MPQ) [37]

[c]Pain intensity rating categories of mild, moderate and severe were set according to previous research on disabilities[23]

[d] Clinically meaningful findings for the Female Sexual Function Index (FSFI) were evaluated with the cut-off score of ≥26.55 indicating low risk of sexual dysfunction[38]

[e] A score of <15 on the Female Sexual Distress Scale (FSDS) is the clinical cut-off for low risk of sexual distress[26]

[f] Number needed to treat (NNT) calculated for none/mild pain.

FIGURE CAPTIONS

Figure 1 title

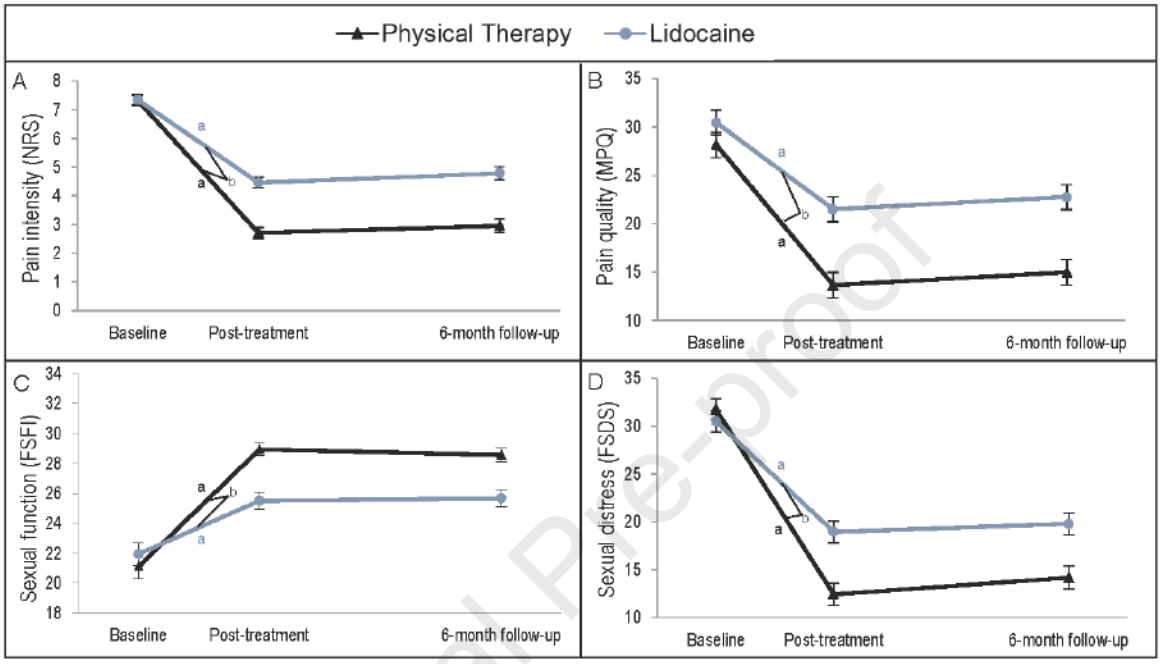
Figure 1 CONSORT Diagram

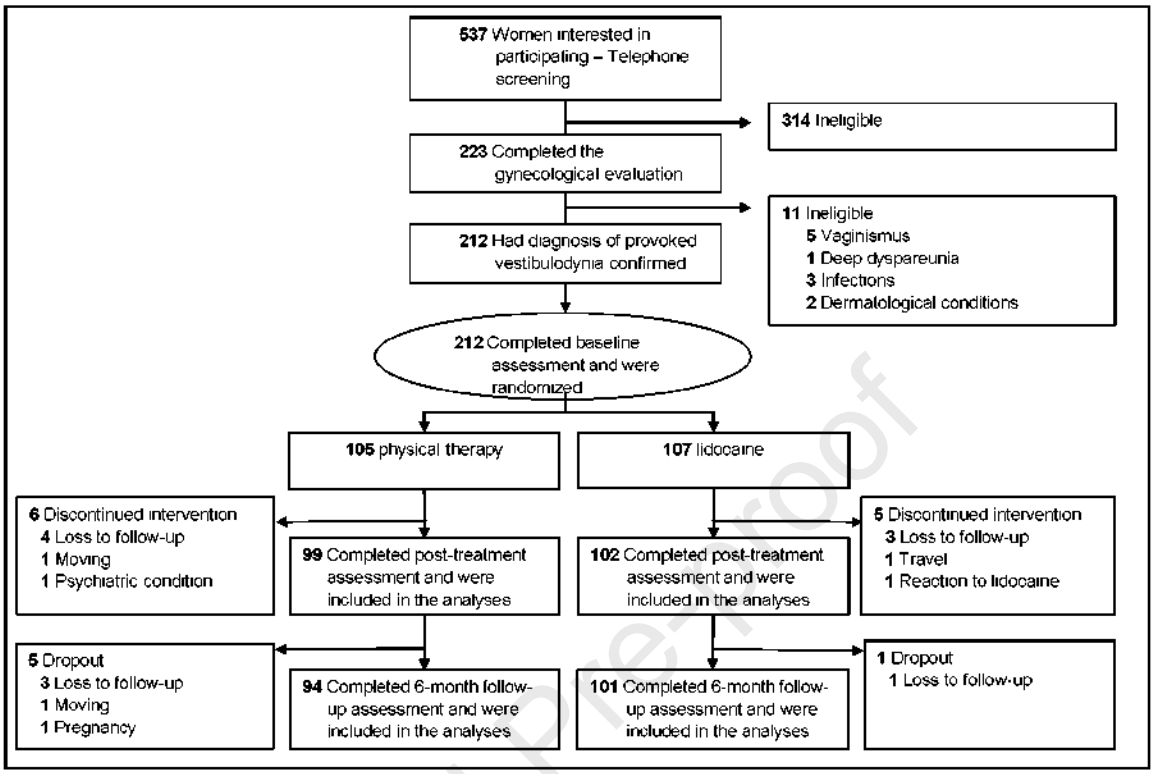
Figure 2 title

Figure 2. Mean estimated scores of pain intensity, pain quality, sexual function and sexual distress over time according to treatment groups.

Figure 2 caption

Figure 2 shows the mean estimated values over time according to treatment group. The mean pain intensity is measured on a numerical pain rating scale (NRS) (scores range from 0 to 10; with 0 indicating no pain and 10 the worst possible pain) (Panel A). The mean pain quality is evaluated with the McGill-Melzack Pain Questionnaire (MPQ) ranging from 0-78, higher values indicating worst pain (Panel B). Sexual function as assessed with Female Sexual Function Index (FSFI) ranges from 19-110 with higher values denoting better sexual functioning (Panel C). Sexually related distress is evaluated with the Female Sexual Distress Scale (FSDS) (range 0-52; higher values being related to more distress) (Panel D). Mean values, standard error and P-values are derived from the multilevel model of change. I bars indicate standard error. [a] denotes significant within-group slope P<.001. [b] represents between-group significant difference (difference in treatment slopes) P<.001.





Credit Author Statement

Conceptualization: Morin, Dumoulin, Bergeron, Mayrand, Khalifé, Waddell, Dubois.

Methodology: Morin, Dumoulin, Bergeron, Mayrand, Khalifé, Waddell, Dubois.

Investigation: Morin, Dumoulin

Writing - Original Draft : Morin

Writing - Review & Editing: Morin, Dumoulin, Bergeron, Mayrand, Khalifé, Waddell, Dubois.

Formal analysis: Morin, Dubois.

Obtained funding: Morin, Dumoulin, Bergeron, Mayrand, Khalifé, Waddell, Dubois.

Project administration: Morin, Dumoulin.

Supervision: Morin, Dumoulin.

Validation: Morin (training of interventionists for physiotherapy).