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I, Catrina C Crisp M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research.

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Intra-vaginal Diazepam for High Tone Pelvic Floor Dysfunction: A Randomized Placebo-Controlled Trial

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Intra-Vaginal Diazepam for High Tone Pelvic Floor Dysfunction: A Randomized Placebo-Controlled Trial

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by

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ABSTRACT

Introduction and Hypothesis:

Intra-vaginal diazepam suppositories are commonly prescribed as a treatment option for high tone pelvic floor myalgia. This triple-blinded placebo-controlled randomized trial sought to determine if 10mg diazepam suppositories improve resting pelvic floor electromyography (EMG) as compared to placebo.

Methods:

Women ≥ 18 years of age diagnosed with hypertonic pelvic floor muscles on exam, confirmed by resting EMG ≥ 2.0 microvolts (μV), administered vaginal suppositories containing either diazepam or placebo for 28 consecutive nights. Outcomes included vaginal surface EMG (4 measurements), the Female Sexual Function Index (FSFI), the Short Form Health Survey 12 (SF-12), 4 visual analog scales (VAS), the Patient Global Impression of Severity (PGI-S), and the Patient Global Impression of Improvement (PGI-I). Our a priori sample size calculation indicated that 7 subjects in each group could detect a $2\mu\text{V}$ difference in resting EMG tone with 90% power.

Results:

Twenty-one subjects were enrolled. The mean age was 36.1 (SD 13.9) years, mean body mass index (BMI) was 28.56 (SD 9.4), and the majority (85.7%) was Caucasian. When evaluating response to therapy, no difference was seen in any of the resting vaginal EMG assessments at any time point within subjects or between groups, nor was an interaction found. Additionally, no differences were noted in any of the validated questionnaire score.

Conclusions:

When used nightly over 4 weeks, vaginal diazepam was not associated with improvement in resting EMG parameters or subjective outcomes when compared to placebo. This suggests a lack of evidence for routine use of diazepam suppositories alone in treating high tone pelvic floor dysfunction.

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INTRODUCTION

Pelvic floor disorders encompass a variety of conditions including pelvic organ prolapse, urinary incontinence and urgency, vulvar disease, dyspareunia, and fecal incontinence. Within this broad scope, a subset of patients exists who suffer from a condition known as high tone pelvic floor dysfunction (HTPFD), or levator myalgia. These women present with pelvic pain characterized by an increase in pain with internal vaginal examination or penetration which may lead to unprovoked vaginal pain due to levator hypercontractility.

While the prevalence of HTPFD is unknown, it is largely believed to be under diagnosed [1].

Contributing factors include an elusive presentation, anxiety or embarrassment causing hesitation in seeking care, and lack of provider awareness of the condition. An experienced examiner and an appropriate index of suspicion are required to identify the condition. Current treatment regimens include pelvic floor physical therapy [2, 3], biofeedback [4], behavioral modification, medications such as antidepressants, acupuncture [5], and trigger point injections [6]. Recently, treatments, such as intra-vaginal diazepam used off-label, have shown a suggested benefit in HTPFD. Nevertheless, the literature surrounding diazepam use is limited [1].

Therefore the purpose of this study was to evaluate the use of intra-vaginal diazepam suppositories compared with placebo for the treatment for HTPFD. We hypothesized that diazepam suppositories used nightly for 28 consecutive nights would decrease resting pelvic floor tone when evaluated by electromyography (EMG). Secondary outcomes included sexual function, pain, and health related quality of life measured using validated questionnaires.

MATERIALS AND METHODS

This was a triple-blinded randomized placebo-controlled trial. The principal investigator, study subjects, data collectors, and the statistician were all blinded to the randomization allocation until completion of all statistical analysis. Local institutional review board approval was obtained, and the study was registered through the U.S. National Institutes of Health Clinical Trials Registry, NCT01233791. All participants gave written informed consent and were limited to the patients of the Division of Urogynecology and Reconstructive Pelvic Surgery at Good Samaritan Hospital, Cincinnati, Ohio.

Subjects were eligible for enrollment if they were English speaking, at least 18 years of age, and diagnosed with high tone pelvic floor dysfunction by the treating Urogynecologist. Subjects were excluded if they had an allergy to diazepam or any benzodiazepine, were currently receiving pelvic floor physical therapy, had undergone pelvic surgery within three months prior to enrollment, were currently pregnant, used benzodiazepines or alcohol on a regular basis (defined as daily use), or had any contraindication to diazepam. Contraindications include hepatic or renal dysfunction, myasthenia gravis, acute narrow angle glaucoma, severe respiratory insufficiency, or sleep apnea. A history of receiving pelvic floor physical therapy did not preclude inclusion unless treatment occurred in the 6 months prior to enrollment.

Potential candidates were approached by the research nurse or principal investigator and informed of the study. Following consent to participate, all subjects underwent vaginal surface EMG. Vaginal EMG measurements were taken at states of rest and during several exercises of the pelvic floor. These were obtained by one of two trained personnel, the research nurse or principal investigator, in order to

reduce error. A t-shaped, vaginal EMG sensor (Thought Technology Ltd., Quebec, Canada; Figure 1) was used for all EMG measurements. The design and shape of the probe allowed for consistent placement, with the cross bar of the t-shape resting on the perineum when placed appropriately. Following each group of pelvic floor exercises or periods of rest, the sensor was evaluated to ensure it had not moved. If movement had occurred, it was repositioned and the exercises repeated. The assessments included a short (30 second) tonic contraction, 5 rapid contractions, 3 long (60 second) interval contractions, and a long (60 second) tonic contraction. The primary outcome, resting pelvic floor tone, consisted of a series of 4 measurements taken at different points of rest throughout the pelvic floor exercises mentioned above. These included: pre-protocol rest, rest following 5 rapid contractions, rest following 3 long interval contractions, and a final rest period after the 60 second tonic contraction. All EMG measurements were collected using a computer-based system (MyoTrac3, Version 1.2, 1997). As the primary objective was improvement in high tone pelvic floor dysfunction, only subjects with a pre-protocol resting EMG measurement $\geq 2.0\mu\text{v}$ were considered eligible for study completion. Study randomization, to treatment or placebo, was revealed by opening a sequentially numbered, opaque, sealed envelope.

In addition to electromyography measures, several validated questionnaires were completed at baseline. These included the Female Sexual Function Index (FSFI), a quadruple Visual Analog Scale (VAS), the SF-12 Health Survey, and the Patient Global Impression of Severity (PGI-S). These four questionnaires, follow-up vaginal EMG measurements, and the Patient Global Impression of Improvement (PGI-I) were collected at 2 and 4 weeks following onset of suppository usage.

The FSFI is a 19-item, validated questionnaire used to screen subjects for sexual disorders. Six domains are assessed with a maximum overall score of 36. The domains of desire, arousal, orgasm, satisfaction, lubrication, and pain are also scored individually. Subjects with overall scores ≤ 26.55 are considered at risk for sexual dysfunction [7].

The SF-12 Health Survey is a brief version of the SF-36. This general health questionnaire is designed to evaluate a subject's health-related quality of life in a physical and mental component. Subjects scoring above 50 are considered to have average or better health. Scores less than 50 represent less than average quality of life as result of the subject's medical health [8].

Four visual analog scales (VAS) were utilized to assess pelvic pain levels. These were administered in the standard 100mm format with instructions to place an "x" on the line indicating their response to each of the questions. VAS questions queried regarding pain level right now, average or typical pain level, pain level at its best, and pain level at its worst [9].

Subjects also completed two additional items: the Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Improvement (PGI-I). Each of these questionnaires consists of a single question scored using a Likert scale. The PGI-S assesses perceived severity of pain "right now" from normal to severe. The PGI-I assesses perceived improvement from very much better to very much worse. [10, 11]

Both written and verbal instructions for appropriate use and application of the vaginal suppository were provided. Written instructions were given in the form of a Patient Administration Leaflet (PAL; Figure 2). The pharmacist, in coordination with the principal investigator, constructed a PAL specific for intra-vaginal administration of the suppositories. The PAL included a diagram illustrating the posterior fornix as the optimal location for suppository placement. When given verbal instructions, subjects were asked to place the suppository as high in the vagina as possible. Subjects were given the option to place the suppository digitally or with an applicator. Instructions were given to use one suppository every night for 28 consecutive nights before going to sleep. This time of administration was chosen to avoid any theoretical sedative effects from the diazepam. Subjects were given routine precautions for benzodiazepine use including: avoiding operating heavy machinery, no driving after taking the medication, and the potential for drowsiness. Average menstrual cycle length and decreased compliance with longer treatment regimens guided the design for 28 days of treatment.

A written prescription for “suppository A” or “suppository 1” was provided for each participant. All investigators, research nurses, and subjects were blinded to the study arm. The compounding pharmacist was the only individual with knowledge of randomization allocation; pharmacy staff was unaware of the randomization key. The pharmacy was located off-site. A map and directions were given if the patient preferred to obtain the suppository from the pharmacy, or the suppository could be shipped directly to their home. The suppositories were white in color, weighed about 2 grams each, and contained 10mg of diazepam. Diazepam is a benzodiazepine known for treatment of muscle spasms, status epilepticus, acute alcohol withdrawal, and anxiety. The onset of action is variable depending on the route of administration. The half life of the medication has a wide range, 20 to 100 hours, with longer elimination required for those with renal or hepatic dysfunction. Notwithstanding, the onset of

action and half life of vaginally administered diazepam has not been determined. Diazepam powder was supplied to the pharmacist by Professional Compounding Centers of America (Houston, TX). Both diazepam and placebo formulations used an identical polyethylene glycol base commonly used for rectal and vaginal suppositories. There was no visual difference between the active and placebo suppositories, and absorption of the base was designed to be similar.

In order to compensate the subjects for their time and travel, a stipend of \$100 was provided following the final study visit. Funding was provided through an educational grant from the TriHealth Good Samaritan Hospital's Medical Education Research Fund.

An a priori sample size calculation indicated 14 patients would be needed to detect a difference of 2 μ v in resting EMG measurement with a power of 90% and a significance level of 0.05 (nQuery Advisor, version 7.0, Statistical Solutions, Saugas, MA, USA). This difference was selected as a clinically relevant change based on physical therapy literature and expert opinion from three pelvic floor physical therapists [12-14]. The randomization schedule was created using nQuery Advisor with a 1:1 ratio using mixed blocks. Descriptive statistics were calculated for demographics and dependent variables. A repeated measures ANOVA was calculated for variables obtained at multiple time points. All statistics were calculated using IBM SPSS Statistics v.19 (SPSS Inc., an IBM Company, Chicago, IL).

RESULTS

Twenty-one patients were approached to participate between September 2010 and December 2011; all agreed to enroll in the study. Eleven were randomized to placebo and 10 to Diazepam (CONSORT Flow Diagram, Figure 3). One patient in the placebo group did not return for the first study visit. One patient in each group was lost to follow up, and two subjects in each group were excluded due to a baseline pre-protocol EMG measurement of less than $2\mu\text{v}$. Thus, 14 subjects completed the study; 7 received diazepam and 7 placebo. The majority was Caucasian (85.7%), with a mean age of 36.1 (SD 13.9), and a mean body mass index (BMI) of 28.56 (SD 9.4) (Table 1). The pelvic organ prolapse quantification exam (POPQ) revealed little to no prolapse for the group. A large number (57%) had a history of depression or anxiety, with the majority taking medication for their condition.

Average baseline EMG measurements for pre-protocol rest was $3.16\ \mu\text{v}$ (SD .88) for the diazepam arm and $2.7\ \mu\text{v}$ (SD .34) for the placebo arm. There was no difference between groups at baseline for any of the four resting measures (Table 2). Using the quadruple VAS, patients reported their pelvic pain at time of office visit to be 4.0, average pain to be 5.5, best pain level 2.0, and worst pain level 8.7 (Table 2). Again, no difference between groups was found at baseline. When evaluating the SF-12, we found that both the physical and mental component scores indicated a lower than average quality of life as a result of their health status. Mean scores for the physical and mental components of the SF-12 for all subjects were 40.4 (SD 14.9) and 39.3 (11.5) (Table 2). The FSFI was utilized to investigate baseline sexual function. Not surprisingly, the total FSFI score for the group was quite low, with a median total score of 13.4 (IQR 9.6, 17.2) (Table 2).

Outcome measures were analyzed using repeated measures ANOVA or analogous non-parametric procedures where appropriate. For all resting vaginal EMG measurements, diazepam did not significantly improve resting tone. There was no interaction effect noted nor was there a difference within groups (Table 3). However, between groups ANOVA revealed a significant difference in two of the four measures: rest period following rapid contractions and post-protocol rest. The between groups ANOVA eliminates the variable of time and averages all three data collection points into one measurement. Surprisingly, this difference favored the placebo group.

Scores on the validated questionnaires were then assessed for the different time points. When evaluating the PGI-I, there was no interaction and no significant difference within subjects or between groups (Table 3). However, when evaluating the PGI-S there was a significant improvement within subjects ($p=0.002$), giving evidence to suggest that care and attention by a provider may have a therapeutic role.

For the SF-12, both the active and placebo groups improved over time in the mental and physical scores. This change, however, was not significant, and there was no difference between groups nor was an interaction effect noted (Table 3). Modest improvements were noted in the VAS for pain. Scores for “pain level right now” and “pain level at its worst” improved for both groups, although this was not found to be significant. The repeated measures evaluation of the FSFI showed no difference within subjects or between groups at any of the three measurement times (Table 3).

DISCUSSION

This triple-blinded randomized placebo-controlled trial investigated vaginal diazepam suppositories as a treatment option for patients with HTPFD. In this study, there was no difference in resting EMG measures after 28 days of use. The diazepam arm also failed to show significant improvements in several quality of life indices such as the FSFI, SF-12, VAS, Patient Global Impression of Improvement, and the Patient Global Impression of Severity.

While previous research in this area is limited, our study contradicts that which exists to date. Rogalski et al. reported improvements in muscle tone using perineometry during three phases: resting, squeezing, and relaxation following squeeze with the use of vaginal diazepam [1]. The study was retrospective, had no control arm, and subjects were undergoing concurrent pelvic floor physical therapy and intramuscular trigger point injections. The confounding effects of parallel treatments as well as the retrospective design may have led to potential bias that could explain the disparate findings. Nevertheless, Rogalski's paper did provide reassurance as to the low risks of side effects related to intra-vaginal diazepam use.

The majority of the literature surrounding HTPFD documents pelvic floor physical therapy and trigger point injections as the mainstay of therapy [15]. Current reported success of trans-rectal massage of the pelvic floor approximates 61% [16]. While trigger point injections are often less effective, up to 33% of subjects may be pain free after this modality [17]. Our results show that intra-vaginal diazepam is a poor substitute for these types of treatment.

Regardless of treatment arm, we did document an improvement in the patients' impression of pain severity, improvement in the subjects' overall health related quality of life from physical and mental aspects, and improvement in pain levels for average pain and worst pain. Possible explanations include a potential for treatment effect in both groups and the influence of provider care and attention. Often, the impact of talking with patients and validating their pain is therapeutic in itself. Further research on this influence on subjects with chronic pain would be of use.

There are several strengths to the study. Subjects were required to have high tone pelvic floor muscles not only by physician examination, but also by objective measurement with surface EMG. This confirms the diagnosis, as well as role for treatment, and renders the study findings reproducible. Outcome measures were both objective and subjective, with use of EMG measurements and questionnaire data. Several validated questionnaires were utilized to assess a variety of symptoms including pain and sexual function. Lastly this study was triple blinded. The subjects, investigators, data collectors, and statistician were all blinded to the randomization allocation.

There are limitations to our study. Although we performed an a priori power calculation, it is possible that our sample size was not large enough to detect a true difference. We are not able to verify with certainty that each subject used the suppository as requested, every night for 28 days. It is also feasible that a higher dosage, more frequent dosing, or longer treatment cycle is necessary to appreciate any true improvement in objective or subjective outcomes with diazepam. Evaluation of the raw data revealed a large standard deviation for all resting EMG measurements, possibly contributing to these

unexpected findings. Finally, we did not evaluate use of vaginal diazepam in conjunction with other traditional treatments such as physical therapy and trigger point injections, as was performed in the prior retrospective study [1]. It is possible that such treatments together provide a synergistic benefit that was not measurable in this cohort.

In this study, vaginal diazepam suppositories used for 28 nights did not improve high tone pelvic floor dysfunction when compared to placebo. Therefore, vaginal diazepam should not be used as a substitute for pelvic floor physical therapy or intra-vaginal trigger point injections. Indeed, there is a lack of evidence for routine use of diazepam suppositories alone in treating high tone pelvic floor dysfunction.

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Figure 1. T-shaped vaginal surface EMG sensor (Thought Technology Ltd., Quebec, Canada)

DIAZEPAM-Diazepam has many common uses including therapy to control seizures, anxiety, or acute alcohol withdrawal. It may also be prescribed for other uses as deemed necessary by your physician.

How to Use: Insert ONE vaginal suppository as high in the vagina as possible EVERY night for the duration of the study period. You may use an applicator if desired. Use this medication exactly as prescribed. Do not take it more or less frequently than prescribed.

Side Effects: Drowsiness, dizziness, fatigue, constipation, blurred vision, or headache. Because this medication is given as a vaginal suppository the side effects may be lessened.

Precautions: Do not take this medication if you have narrow-angle glaucoma, a muscle condition known as myasthenia gravis, are pregnant or may become pregnant, have liver or kidney failure, or require oxygen at home for breathing. Avoid products that contain alcohol while using this drug: If overdose is suspected, contact your local poison control center or emergency room.

Missed Dose: If you miss a dose, use it as soon as you remember. If it is near the time for your next dose, resume your normal dosing schedule. Do not double up or use two suppositories.

1. Be sure to wash your hands with mild soap and warm water before insertion.
2. Remove vaginal suppository from packaging and wrapping.
3. Hold the suppository on the end of your index finger.
4. Insert the suppository into the vaginal canal, like inserting a tampon.
5. Be sure the suppository is as far into the vaginal canal as possible.
6. Be sure to wash your hands with mild soap and warm water after insertion.

Figure 2. Patient Administration Leaflet specific for intra-vaginal administration of suppositories

CONSORT Flow Diagram

Figure 3. CONSORT flow diagram

Table 1. Demographics and comparisons for total sample and by group				
	Total Sample	Diazepam	Placebo	<i>p</i> -value
	N=14	N=7	N=7	
Age, mean (SD)	36.1 (13.9)	35.9 (12.0)	36.3 (16.6)	.957*
Race				.769†
Caucasian, n (%)		6 (85.7)	6 (85.7)	
African American, n (%)		1 (14.3)	1 (14.3)	
BMI, mean (SD)	28.56 (9.4)	26.7 (9.2)	30.4 (10.0)	.485*
Marital Status				.967‡
Married, n (%)	7 (53.8)	3 (50.0)	4 (57.1)	
Single, n (%)	4 (30.8)	2 (33.3)	2 (28.6)	
Divorced, n (%)	2 (15.4)	1 (16.7)	1 (14.3)	
Gravida, median (IQR)	2 (0, 3.25)	2 (0, 6)	2 (0, 3)	1.000§
* Student's t-test † Fisher's Exact test ‡ Pearson's Chi-square § Independent samples median test				

Table 2. Baseline and group comparisons for EMG, VAS, SF-12, and FSFI				
	Total Sample	Diazepam	Placebo	p-value
	N=14	N=7	N=7	
Electromyography (EMG) measures				
Pre-protocol Resting Average (μ V), mean (SD)	2.93 (0.68)	3.16 (0.88)	2.70 (0.34)	.238*
Resting Average after Rapid Contractions(μ V), mean (SD)	2.61 (0.83)	2.93 (0.78)	2.30 (0.81)	.164*
Resting Average after Long Contractions (μ V), mean (SD)	2.84 (1.19)	3.44 (1.20)	2.24 (0.89)	.054*
Post-protocol Resting Average (μ V), mean (SD)	2.32 (1.16)	2.77 (0.91)	1.87 (1.28)	.155*
Visual Analog Scales (VAS)				
Pain Right Now, median (IQR)	4.0 (0.75, 5.25)	4.0 (1.0, 4.0)	3.0 (0.0, 6.0)	1.000†
Average Pain, median (IQR)	5.5 (3.0, 6.6)	6.0 (4.0, 6.5)	5.0 (3.0, 7.0)	.650†
Pain Level at Best, median (IQR)	2.0 (0.75, 3.0)	1.0 (0.0, 2.5)	3.0 (2.0, 3.0)	.173†
Pain Level at Worst, mean (SD)	8.68 (0.99)	8.50 (0.96)	8.86 (1.07)	.523*
Short-Form Health Survey (SF-12)				
Physical Component Score (PCS), mean (SD)	40.4 (14.9)	46.3 (8.85)	38.7 (14.29)	.317*
Mental Component Score (MCS), mean (SD)	39.3 (11.5)	37.7 (11.48)	40.9 (12.20)	.623*
Female Sexual Function Index				

(FSFI)				
Desire, median (IQR)	2.7 (2.3, 3.0)	2.4 (1.8, 3.0)	3.0 (2.4, 4.8)	.383 [†]
Arousal, median (IQR)	2.1 (1.5, 2.8)	2.1 (1.8, 2.7)	1.8 (0, 3.3)	.456 [†]
Lubrication, median (IQR)	2.1 (0.9, 3.9)	1.8 (1.2, 3.9)	2.4 (0, 3.9)	.805 [†]
Orgasm, median (IQR)	1.2 (0.9, 2.0)	1.2 (1.2, 3.2)	1.2 (0, 1.6)	.805 [†]
Satisfaction, median (IQR)	2.8 (1.7, 4.0)	3.2 (2.0, 5.2)	2.4 (0.8, 3.6)	.710 [†]
Pain, median (IQR)	1.8 (0.0, 2.2)	1.6 (0, 2.0)	2.0 (0, 4.8)	.318 [†]
Total, median (IQR)	13.4 (9.6, 17.2)	13.5 (11.9, 16.8)	13.4 (5.6, 20.5)	1.00 [†]

Table 3. Analysis of variance for EMG, Patient Global Impression scales, SF-12, VAS, and FSFI

Table 3. Analysis of variance for EMG, Patient Global Impression scales, SF-12, VAS, and FSFI									
	Baseline		2-week		4-week		Significance*		
	Diazepam	Placebo	Diazepam	Placebo	Diazepam	Placebo	Within Subjects ¹	Interaction ²	Between groups ³
EMG Measurements									
Pre protocol resting average, μ V, mean (SD)	3.16 (.88)	2.7 (.34)	3.33 (.99)	3.2 (2.17)	3.44 (1.03)	2.38 (1.58)	.608	.498	.319
Post rapid contractions resting average, μ V, mean (SD)	2.93 (.78)	2.30(.81)	3.13 (1.07)	2.51 (1.49)	3.33 (1.18)	1.80 (.84)	.749	.355	.035
Post long contraction resting average, μ V, mean (SD)	3.44 (1.20)	2.24 (.89)	3.60 (1.44)	2.49 (1.94)	3.08 (1.48)	2.38 (1.94)	.819	.523	.165
Post protocol resting average, μ V, mean (SD)	2.77 (.91)	1.87 (1.28)	2.67 (1.05)	1.77 (1.34)	2.86 (1.48)	1.38 (.83)	.842	.630	.045
Patient Global Impression Scales									
PGI-I, mean (SD)	n/a	n/a	3.50 (.84)	2.86 (.90)	3.67 (1.03)	2.71 (1.11)	1.000	.357	.154
PGI-S, mean (SD)	2.67 (.52)	3.00 (.82)	2.33 (.52)	2.00 (.82)	2.08 (.80)	2.14 (.69)	.002	.268	.952
Short-Form Health Survey (SF-12)									
Physical Component Score	45.13 (17.26) N=5	37.78 (14.17) N=7	46.31 (8.84) N=5	38.66 (14.29) N=7	47.63 (15.20) N=5	41.30 (14.82) N=7	.484	.962	.389
Mental Component Score	36.88 (13.92) N=5	40.94 (12.20) N=7	38.89 (15.56) N=5	42.02 (13.90) N=7	39.35 (18.49) N=5	47.70 (13.19) N=7	.315	.569	.512
Visual Analog Scales (VAS)									
Pain right now, median (IQR)	4 (1, 4)	3 (0, 6)	3.5 (1.5, 5)	1 (0, 3)	3.5 (1.5, 5.25)	1 (0, 5)	.165†	n/a	1.00†§ .234† .455†¶
Average pain, median (IQR)	6 (4, 6.5)	5 (3, 7)	5 (4, 5.25)	4 (2, 5)	5 (4, 5.5)	4 (1, 5)	.794†	n/a	.710†§ .366† .286†¶
Pain level at best, median (IQR)	1 (0, 2.5)	3 (2, 3)	2.5 (1.75, 3)	1 (0, 2)	2 (0, 3.5)	1 (0, 1)	.779†	n/a	.209†§ .101† .639†¶
Pain level at worst, mean (SD)	8.42 (1.02) N=6	8.86 (1.07) N=7	8.5 (1.22) N=6	7.29 (2.14) N=7	8.00 (1.90) N=6	6.71 (2.69) N=7	.047	.155	.431
Female Sexual Function Index									
FSFI Desire, median (IQR)	2.4 (1.8, 3.0)	3.0 (2.4, 4.8)	3.6 (2.4, 3.6)	2.4 (2.4, 3.6)	3.0 (1.6, 3.6)	3.0 (1.8, 3.0)	.350†	n/a	.383§ .366 1.000¶

FSFI Arousal, median (IQR)	2.1 (1.8, 2.7)	1.8 (0, 3.3)	1.0 (0, 2.8)	2.7 (0.6, 3.0)	1.5 (0.7, 3.4)	1.8 (0, 3.6)	.933†	.n/a	.456\$.366 .836¶
FSFI Lubrication, median (IQR)	1.8 (1.2, 3.9)	2.4 (0, 3.9)	1.2 (0, 3.0)	3.0 (0, 3.3)	1.2 (0, 3.0)	1.8 (0, 4.8)	.549†	.n/a	.805\$.295 .432¶
FSFI Orgasm, median (IQR)	1.2 (1.2, 3.2)	1.2 (0, 1.6)	0 (0, 3.2)	2.8 (0, 2.8)	1.6 (0, 2.4)	1.2 (0, 2.0)	.296†	.n/a	.805\$.445 1.000¶
FSFI Satisfaction, median (IQR)	3.2 (2.0, 5.2)	2.4 (0.8, 3.6)	0.8 (0, 3.0)	2.8 (0, 4.4)	2.4 (0, 4.2)	3.2 (0, 4.4)	.433†	.n/a	.710\$.295 .628¶
FSFI Pain, median (IQR)	1.6 (0, 2.0)	2.0 (0, 4.8)	0 (0, 1.0)	3.2 (0, 3.38)	0 (0, 2.2)	2.8 (0, 4.4)	.587†	.n/a	.318\$.240 .101¶
FSFI Total, median (IQR)	13.5 (11.9, 16.8)	13.4 (5.6, 20.5)	7.0 (2.4, 17.3)	17.2 (4.6, 18.9)	9.5 (3.2, 15.2)	13.9 (4.8, 23.6)	.526	.n/a	1.000\$.240 .268¶

1=Within subjects analyses compare all subjects at baseline with all subjects after treatment (i.e., pre-treatment versus post-treatment analysis)

2=Interaction analyses describe how each group changes differentially over time (i.e., differential slope lines)

3=Between group analyses compare all subjects in the control arm to all subjects in the treatment arm (i.e., time is not a factor)

* Except where noted otherwise, by repeated measures analysis of variance

†Related-samples Friedman's two-way analysis of variance

‡Independent-samples Mann-Whitney U test

\$ Baseline

|| Two week

¶ Four week