Unique Protocol ID:	1208827
Brief Title:	Vaginal Diazepam for the Treatment of Female Pelvic Pain
Official Title:	Intravaginal Diazepam for the Treatment of Pelvic Pain Among Women With Pelvic Floor Hypertonic Disorder: a Double Blind, Randomized, Placebo Controlled Trial
Version:	5
Date:	08/18/2016

Intravaginal diazepam for the treatment of pelvic pain among women with pelvic floor hypertonic disorder: a double blind, randomized, placebo controlled trial

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ABSTRACT

OBJECTIVE: To determine the efficacy of intravaginal diazepam for the treatment of pelvic pain associated with pelvic floor hypertonic disorder.

METHODS: After informed consent, women 18 years of age or older presenting with pelvic pain and physical exam findings of levator spasm will be scheduled to receive a standard therapy consisting of a bowel regimen, heat therapy, kegel exercises, and pelvic stretching exercises for 4 weeks. Subjects will then be randomized by a computer-derived random number sequence to receive either a self-administered program of intravaginal diazepam 10 mg one-two times daily, or a placebo vaginal tablet during the 4 weeks of their standard therapy. At the end of the 4 weeks, patients will be allowed to enroll in a program of comprehensive pelvic floor rehabilitative therapy (CPRFT) we have described previously [3]. Pelvic floor pain and response to treatment will be evaluated by the Visual Analog Scale for Pain (VAS-P) and validated questionnaires. Using improvement in the VAS-P as our primary outcome, seventeen women in each group will be required to achieve 80% power to detect a difference of patient's perceived level of improvement of symptoms. In order to account for patients lost to follow-up, 25 patients will be enrolled in each group. Outcomes will be assessed at baseline, 4 weeks, 12 weeks, and 24 weeks. Patients, care-givers and those assessing the outcomes will be blinded to group assignment.

ANTICIPATED RESULTS AND CONCLUSIONS: These authors predict that the initial group of patients randomized to receive intravaginal diazepam will demonstrate a significant improvement in their Visual Analog Scale for Pain scores (VAS-P) from baseline. We also predict that women from either group who enroll in the program of CPFRT will have superior outcomes than those who do not enroll in CPFRT.

TRIAL REGISTRATION: This trial will be registered at clinicaltrials.gov pending IRB approval

FUNDING: The primary investigator will be using his faculty start-up funding for miscellaneous expenses related to this project

INTRODUCTION

Pelvic floor hypertonic disorder, (a.k.a. high-tone pelvic floor dysfunction, levator spasm, pelvic floor muscle spasm, myofascial pelvic pain, etc.) represents a neuromuscular condition characterized by involuntary levator spasm and reproducible pain upon vaginal penetration and internal examination [1]. It may manifest as a primary pain generator, a singular component of chronic pain, or a dysfunction of viscera (bladder or bowel) controlled by the pelvic floor musculature. Clinical syndromes associated with pelvic floor hypertonic dysfunction are numerous and include childhood elimination disorder, idiopathic urinary retention, vaginismus, constipation, pelvic floor dyssynergia, bladder pain syndrome/interstitial cystitis, vulvodynia, colorectal pain, and chronic pelvic myofascial pain syndrome [2].

Although a number of non-surgical treatment options are described in the literature (pelvic floor physical therapy and rehabilitation, botulinum toxin injections, pharmacological therapy, off-labeled use of intravaginal diazepam), data describing their efficacy is limited [2]. For example, a recent retrospective review we recently published, analyzing the efficacy of a comprehensive pelvic floor rehabilitation program (CPFRP) on pelvic floor disorders demonstrated an 80% improvement in urinary, defecatory, and pain disorders throughout a 5-session course of rehabilitation [3]. Unfortunately, this treatment modality has limitations due to its cost and accessibility to geographically isolated patients. Previously, a randomized controlled trial comparing Botulinum Toxin Type A to placebo did not demonstrate any statistically significant improvement in either the Visual Analog Pain Scale or quality of life in patient's treated with Botulinum Toxin [4].

Intravaginal diazepam has generated interest as a viable alternative to traditional pelvic floor physical therapy. A retrospective study in patients receiving diazepam vaginal suppositories in adjunct to pelvic physical therapy and intramuscular trigger point injections reported a clinically significant, but not statistically significant level of subjective improvement in 25 of 26 patients [5]. Recently, a randomized controlled trial by Crisp et al. using a nightly dose of 10 mg intravaginal diazepam, failed to demonstrate a significant improvement in resting EMG parameters or subjective outcomes when compared with placebo. However, this study has limitations with sample size and dosing schedule.

The purpose of this study is to evaluate the efficacy of intravaginal diazepam in the treatment of pelvic pain among women with hypertonic pelvic floor disorder. Secondary outcomes will include assessment of CPFRT efficacy as adjunctive or stand-alone therapy for the treatment of hypertonic pelvic floor disorder. We hypothesize that patients receiving self-administered intravaginal diazepam, one to two times daily, in addition to a standard conservative therapy consisting of a psyllium-based bowel regimen, heat therapy, pelvic stretching and kegel exercises, will demonstrate a significant improvement

in pain scores after 4 weeks compared to those patients receiving the standard conservative therapy alone. We then hypothesize that patients enrolling in a program of comprehensive pelvic floor rehabilitation therapy will increase their pain improvement scores after 12 and 24 weeks compared to those patients receiving intravaginal diazepam plus standard conservative therapy alone. Additional secondary outcomes of interest include sexual function, pain, and health-related quality of life as measured by validated questionnaires.

METHODS

This is a double blind, randomized, placebo controlled trial. This is a single site study that will include women being seen at a MU Health Clinic site with complaints of acute or chronic pelvic pain will be approached for enrollment into this research protocol.

Inclusion criteria:

1. Age 18 years or older
2. Primary complaint of acute or chronic pelvic pain with or without dyspareunia
3. Physical exam findings consistent with levator muscle spasm

Exclusion criteria:

1. Chronic narcotic use
2. Non-English speaking
3. Currently serving a prison sentence
4. Stage III or greater vaginal prolapse
5. Allergies or contraindications to benzodiazepines
6. Pregnant or breastfeeding
7. Current or previous treatment with CPFRT and/or vaginal valium therapy

Participating women will be scheduled to receive a standard conservative therapy consisting of a psyllium –based bowel regimen, heat therapy, pelvic stretching exercises, and kegel exercises [3]. Patients will be randomly assigned (after pregnancy is ruled out by a urine pregnancy test performed in the office) to either the treatment group (intravaginal diazepam) or the placebo group (investigators and patients will be blinded to group assignment by use of sequential opaque envelopes). The diazepam capsules will be created by the investigational pharmacy by embedding hard size 1 gelatin capsules with manufactured diazepam 10mg tablets (Teva Pharmaceuticals) and cellulose filler. Identical appearing gelatin capsules filled only with cellulose will be used for the placebo group.

The diazepam, capsules, and filler will be funded by the primary investigator. The treatment group will receive a self-administered regimen of 10 mg diazepam vaginal capsules to be used one to two times daily as needed in addition to the standard conservative therapy. The placebo group will receive the standard conservative therapy, and an inactive intravaginal tablet. The participants will acknowledge

during the consent process that they will only take the placebo or diazepam capsules vaginally. . After 4 weeks, patients from either group will have the option of enrolling into a program of comprehensive pelvic floor rehabilitation therapy as described previously by Starr et al.

A review of the literature does not report any adverse events from intravaginal diazepam (1,5), and the onset of action and half-life of intravaginal diazepam has not been determined [1]. We will diligently monitor for any unexpected adverse events that may be result of medication.

The primary outcome of interest will be the patient's improvement of pain as measured by the Visual Analog Scale for Pain (VAS-P) at 4 weeks. Secondary outcomes of interest will be the patients' perceived level of sexual function, pain and health-related quality of life as measured by validated questionnaires such as PFDI-20. The VAS-P and questionnaires (PFDI-20, McGill Pain Questionnaire, and Global Response Assessment) will be completed at baseline, 4, 12, and 24 weeks. Patients will be given the option of choosing one or more of the following methods for follow-up contact and data collection: electronic mail, self-addressed home envelope, or telephone call. Case report forms will be utilized by investigators to record data provided by the patients.

The investigational pharmacy will perform the computer-derived randomization and create a log book to track and un-blind the participants in case of an adverse eventThe log book and capsules will be transferred to the dispensing pharmacy, (in-patient pharmacy at Women's and Children Hospital, Columbia, MO) for including the participants. A co-investigator will write a prescription for a 4-week supply (60 capsules). A clinic nurse will take the prescription to the dispensing pharmacy and return with the capsules and give to the participant. Participants will also have the option of having the dispensing pharmacy mail a 4-week supply of capsules directly to the participants.

STATISTICAL METHODS

We will be using a non-parametric 2 sample t-test to compare pain scores between placebo and diazepam groups. Chi-squared analysis will be performed to calculate the proportion of patients analyzed in each of four CPFT groups (CPFT alone, CPFT + diazepam, CPFT + placebo, placebo alone). In order to determine the treatment response and variance for use in power calculation for our primary outcome of VAS pain scale at 4 weeks, 4 placebo-controlled studies were evaluated that used VAS-P to assess the response of pelvic pain to treatment. Results from those using a 10 point VAS were converted to a 100 point scale.

Paper	Baseline	Placebo	Treatment	Difference (mm)
Harada et al [6]	78 ± 13	53 ± 6	27 ± 13	26
Bergqvist et al [7]	58 ± 12	43 ± 8	08 ± 10	35
Abbott et al [2]	52 ± 19	40 ± 20	25 ± 20	15
Seracchioli et al [8]	40 ± 38	30 ± 49	0 ± 11	30

Results are mean ±SD or median ± interquartile range. Values were estimated by measurements from the published graph when exact values were not presented.

Assuming a difference in VAS between treatment and placebo of 20 mm with a SD of 20 mm, 17 women in the diazepam and placebo groups will be required to give 80% power and a two-sided 5% significance

level. In order to account for patients lost to follow-up, we will enroll 25 patients per treatment group. To recruit this number of patients, a 6 month inclusion period is anticipated. Fifty patients will be allocated by sealed opaque envelopes according to a computer-derived random number sequence consisting of 25 groups of 2 choices (random.org).

Patients, care-givers and those assessing the outcomes will be blinded to group assignment.

Upon completion of enrollment, data analysis will begin. The investigational pharmacist will provide un-blinded information to the study statistician only. This information will be communicated through a secure password protected file.

EXPECTED RESULTS

Patients randomized to receive intravaginal diazepam will not differ from those randomized to placebo in terms of patient age, duration of pain, psychological and medical history, gynecology problem list, body mass index, and physical exam findings. Patients randomized to receive intravaginal diazepam will have significantly higher improvement scores compared to placebo on the VAS-P. It is anticipated that more patients from the placebo group than the intravaginal diazepam group will enroll into the comprehensive pelvic floor rehabilitation therapy program. It is anticipated that the patients in the comprehensive pelvic rehabilitation therapy group will have higher VAS-P scores then patients receiving either intravaginal diazepam or placebo alone.

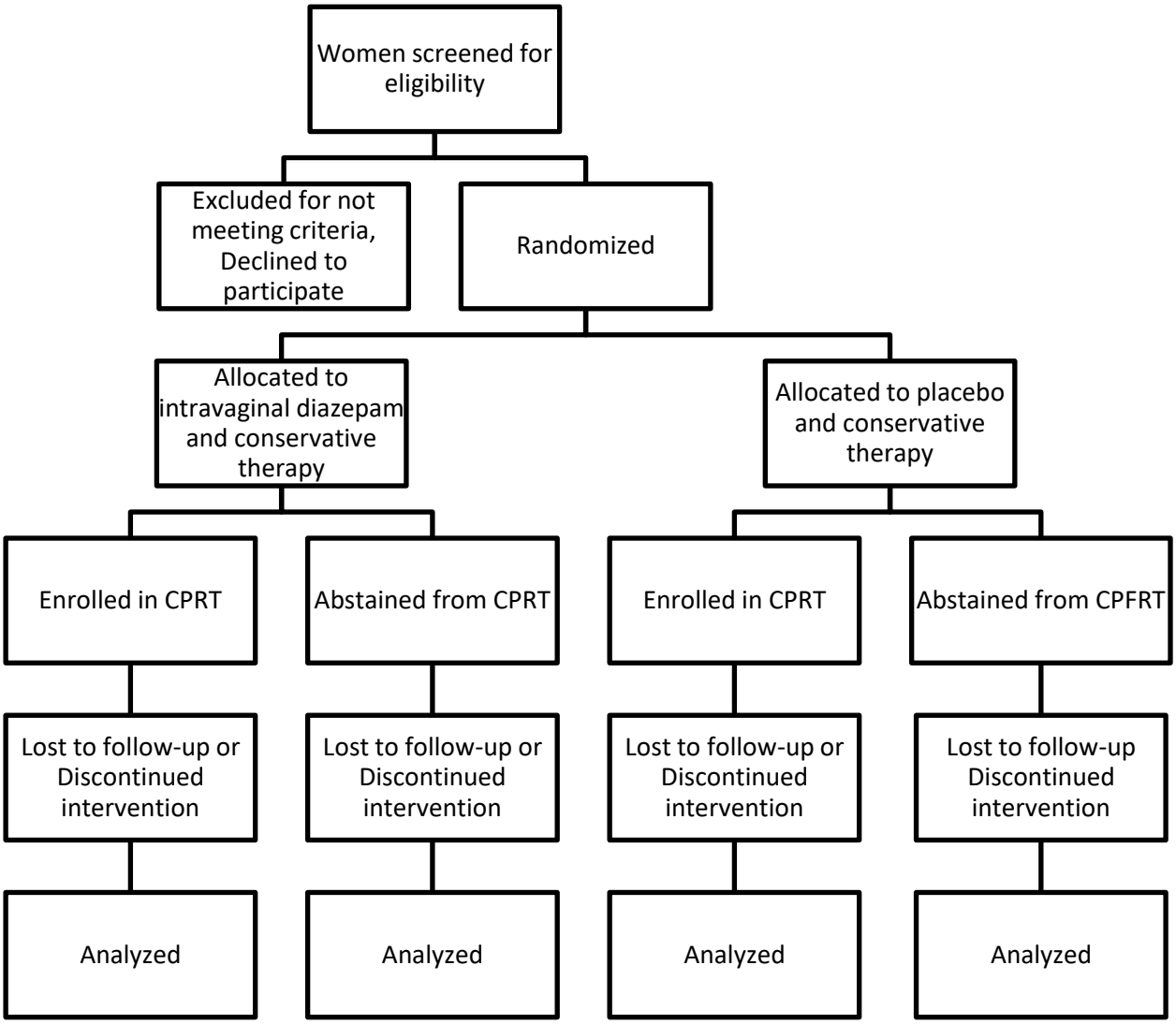
REFERENCES:

1. Crisp CC, Vaccaro CM, Estanol MV, Oakley SH, Kleeman SD, Fellner AN, Pauls RN. Intra-vaginal diazepam for high-tone pelvic floor dysfunction: a randomized placebo-controlled trial. Int Urogynecol J. 2013. epublished 17 May
2. Butrick CW. Pelvic floor hypertonic disorders: identification and management. Obstet Clin North Am. 2009;36(3):707-22
3. Starr JA, Drobnis EZ, Lenger S, Parrot J, Barrier B, Foster RT. Outcomes of a comprehensive nonsurgical approach to pelvic floor rehabilitation for urinary symptom, defecatory dysfunction, and Pelvic Pain. Female Pelvic Medicine & Reconstructive Surgery. 2013
4. Abbot JA, Jarvis SK, Lyons SD, Thomson A, Vancaille TG. Botulinum toxin type A for chronic pain and pelvic floor spasm in women, a randomized controlled Trial. Obstet Gynecol. 2006;108 (4)915-23.
5. Rogalski MJ, Kellogg-Spadt S, Hoffmann AR, Fariello JY, Whitmore KE. Retrospective chart review of vaginal diazepam suppository use in high-tone pelvic floor dysfunction. Int Urogynecol J. 2010;21:895-9.
6. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90: 1583-8.
7. Bergqviat A, Bergh T, Hogström L, Mattsson S, Nordenskjöld F, Rasmussen C. Effects of

triptorelin versus placebo on the symptoms of endometriosis. Fertility and Sterility. 1998; 69(4):702-8.

8. Seracchioli R, Mabrouk M, Frascà C, Manuzzi L, Savelli L, Venturoli S. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. Fertil Steril. 2010;94: 464-71.

Flow diagram of patient disposition throughout the study.


Women screened for eligibility
Excluded for not meeting criteria, Declined to participate
Randomized
Allocated to intravaginal diazepam and conservative therapy
Allocated to placebo and conservative therapy
Enrolled in CPRT
Abstained from CPRT
Enrolled in CPRT
Abstained from CPFRT
Lost to follow-up or Discontinued intervention
Lost to follow-up or Discontinued intervention
Lost to follow-up or Discontinued intervention
Lost to follow-up Discontinued intervention
Analyzed
Analyzed
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