

Experimental pain sensitivity in women with vestibulodynia: a pilot study

Laura Frey Law, MPT, MS, PhD.,¹ Avery Whitis, BS.,² Colleen K. Stockdale, MD, MS³

Keywords: Pain sensitivity, vestibulodynia, vulvodynia, pressure pain thresholds, hyperalgesia, central sensitization

Abstract

Objective: Investigate pain sensitivity in women with vestibulodynia using two experimental pain assessments outside the vulvar region: intramuscular infusion of an acidic phosphate buffer and pressure pain thresholds (PPTs) of the lower limb.

Methods: Three women with a history of vestibulodynia (all 24 years old) participated after providing written informed consent. PPTs of the lower limb were assessed using a hand-held Somedic digital algometer (30 kilopascal (kPa)/sec) at baseline (pre-infusion) and during the intramuscular infusion. The acidic phosphate buffer (pH 5.2) was infused into the anterior tibialis muscle at a rate of 40 ml/hr for 15 min (10 ml total). Peak local (infusion site) and referred (ankle) pain ratings were assessed verbally, as well as vulvar pain at the time of the infusion (0 – 10 Borg Scale).

Results: Peak local pain was higher in two of the three subjects (2.5, 4.0, 9.5) than the average pain ratings in 34 healthy age-matched (21 – 27 years old) women from our laboratory, mean 3.0/10 (standard deviation (SD) 2.2; range 0.5 to 10). Peak referred pain was also higher in the

same two subjects (0, 4.25, and 7.5) than the average of the controls (mean 1.5; SD 1.8; range 0 – 9.0). Similarly, vulvar pain patients all exhibited greater mechanical pain sensitivity (lower PPT values) than the average of the healthy controls (mean [SD] 246.3 [101.7] kPa in patients vs. 431.3 [109.33] in controls).

Conclusion: Preliminary data suggests women with vestibulodynia may exhibit greater generalized pain sensitivity to noxious stimuli than the general population of women.

¹Department of Physical Therapy and Rehabilitation Science, University of Iowa, Iowa City, Iowa

²University of Iowa Carver College of Medicine, Iowa City, Iowa

³University of Iowa Hospitals and Clinics, Department of Obstetrics and Gynecology, Iowa City, Iowa

Introduction

Pain in the United States is an enormous problem that leads to impairment and disability, resulting in social and economic consequences for

Please cite this paper as: Frey Law L, Whitis AM, Stockdale CK. Experimental pain sensitivity in women with vestibulodynia: a pilot study. *Proc Obstet Gynecol.* 2017;7(1): Article 3 [8 p.]. Available from: <http://ir.uiowa.edu/pog/> Free full text article.

Corresponding author: Colleen Stockdale, MD, MS, Department of Obstetrics and Gynecology, 200 Hawkins Drive, Iowa City, IA 52246, Phone: 319-384-6849, Fax: 319-384-8620. Email: colleen-stockdale@uiowa.edu

Financial Disclosure: The authors report no conflict of interest.

Copyright: © 2016 Frey Law et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

both the individual and society. Thirty-four million Americans suffer from chronic pain. The cost for relief for back pain, migraines, and arthritis alone exceeds \$40 billion annually.¹ Pain is cited as the primary reason for 50 million work days lost per year.¹

Pain is highly multidimensional, leading to differing sensations depending on origins from musculoskeletal tissue, soft tissue, or cutaneous regions.² Human pain perception varies greatly between individuals and results from the integration of unique objective, sensory, cognitive, and affective processes.³ Other contributing factors to the experience of pain are central and peripheral sensitization.⁴ Central sensitization refers to enhanced neural responsiveness within the dorsal horn of the spinal cord and prolonged C fiber activity. Peripheral sensitization refers to the lowered nociceptor threshold for stimulation. There are growing interests to better understand the individual differences in central and peripheral contributions to pain perception and tolerance, ultimately to lessen the burden of pain management.

Experimental pain provides the unique opportunity to investigate pain sensitivity through the use of controlled noxious stimuli. Methods to induce experimental pain are categorized as endogenous and exogenous.⁶ Endogenous methods involve activating pain without the exposure of an external substance, such as isometric or eccentric exercises to induce tissue hypoxia. Exogenous methods involve the use of external stimuli, such as electrical or chemical stimulation of nociceptors.⁶ Hypertonic saline and acidic saline injections are exogenous models used to produce

temporary myalgias, with no adverse side effects reported over thousands of infusions, suggesting technique safety.⁷ Frey Law, et al., studied central sensitization using an acidic buffer infusion (pH 5.2) and found that muscle acidosis produced light to moderate, and rate-dependent, muscular pain at the site of infusion as well as referred pain in a distant site compared to control infusions.⁸ Sluka, et al., also found that an acidic infusion into muscular tissue can produce hyperalgesia in animal models, with maximum activation of nociceptors occurring at a pH of 5.2, and consistent activation at a pH of 6.0.⁹ Thus, an acidic infusion pain model can be used to examine both local and referred pain safely in humans.

Vulvodynia is a chronic pain disorder characterized by increased sensitivity of external stimuli at the vulva and/or spontaneous vulvar pain in the absence of disease pathology.¹⁰⁻¹³ The pain is often described as knife like, burning, irritation or itching, and can be provoked or unprovoked.^{10, 11} Lifetime prevalence of vulvodynia is 10-15% in the United States and cost of care in the USA has been cited as being greater than \$8000 per patient for a 6 month course of treatment.¹³ Vulvodynia is thought to be augmented by central sensitization, as evidenced by dynamic vulvar tactile allodynia, body-wide pain threshold reductions, and pain hypervigilance and anxiety.¹⁴ Hampson, et al., further clarified this hypothesis, by showing that women with vulvodynia also experience increased pain perception at peripheral tissues such as the thumb, deltoid, and shin, suggesting that factors remote from the vulva may play a role in symptom perception.¹²

This study aims to investigate pain sensitivity with vestibulodynia using two experimental pain assessments of the lower limb: intramuscular infusion of an acidic phosphate buffer to examine local and referred pain, and pressure pain thresholds before and during the infusion.

Methods

Subjects

Three women with a history of vestibulodynia, all aged 24 years, participated in this pilot study after providing written informed consent as approved by the local Institutional Review Board. Exclusion criteria included history of cardiovascular, neuromuscular diseases, history of diabetes/neuropathy or other immunocompromise, other current chronic pain besides vulvodynia, pregnancy, significant injury to lower extremities, and inability to communicate. Participants were compared to 34 age-matched (21-27 yr.) and sex matched controls. Exclusion criteria for control participants included current pain complaints, past history of chronic pain, significant medical history, prescription medications other than birth control or vitamins, pregnancy, and history of lower extremity injury. Participants were instructed that moderate muscle pain could occur and were reimbursed for their time (1.5 hr per visit).

Study protocol

Subjects participated in two visits, spaced 5-14 days apart. An acidic phosphate buffer was infused into the anterior tibialis muscle at a rate of 40

ml/hr for 15 min, for a total of 10 ml. While hypertonic saline has been used in patient populations (e.g. elbow tendinitis, fibromyalgia, osteoarthritis) this acidic phosphate infusion has not. It is not used as treatment, but as an experimental model to investigate the pain responses elicited by this noxious stimulus. The advantage of acid over hypertonic saline is that it may be more physiologically appropriate (activates ASICs and TRPV1 channels) which are specific to pain nociceptors as opposed to sodium channels which are not specific to pain. Further, this acidic phosphate buffer provides a means that has been repeatedly shown to induce referred pain in about 60% of the population (higher in women), and may be useful for examining this centrally mediated phenomenon in patient populations more specifically.

The acidic buffer was prepared by the local hospital pharmacy with a pH of 5.2 in sterile 30 mL syringes, and was iso-osmotic to saline. Peak local (infusion site) and referred (ankle) pain ratings were assessed verbally before, during, and 20 minutes after infusion, as well as any vulvar pain at the time of the infusion. Pressure pain thresholds (PPTs) of the lower limb were assessed as the average of multiple repetitions using a digital hand-held Somedic digital algometer (30 kPa/sec, 1 cm² tip) at baseline (pre-infusion, n=4 repetitions) and during the intramuscular infusion (n=2 each assessment) (Figure 1). Baseline algometer repetitions were done before and after the insertion of the catheter (2 each) and were found to be the same. Thus, the protocol was collapsed to a single baseline of 4 repetitions. Participants were instructed

to press the hand-held trigger when the pressure first became painful (i.e., “a 1 out of 10”). PPTs were determined at four locations ipsilateral to the infusion (upper and lower anterior tibialis, anterior ankle, and web space between 1st and 2nd metatarsals on the foot) and two mirrored contralateral locations (lower anterior tibialis and ankle). Radial artery pulse at the wrist was measured manually every 5 minutes throughout the 45 minute protocol. For more

information on study protocol and specifics of intramuscular infusions, see Frey Law, et al.⁸

Descriptive statistics (mean, standard error of the mean (SEM)) were calculated for all pain and sensory variables.

Z-scores and percentile ranks for the pain responses were calculated for each patient using the healthy control mean and variance data.

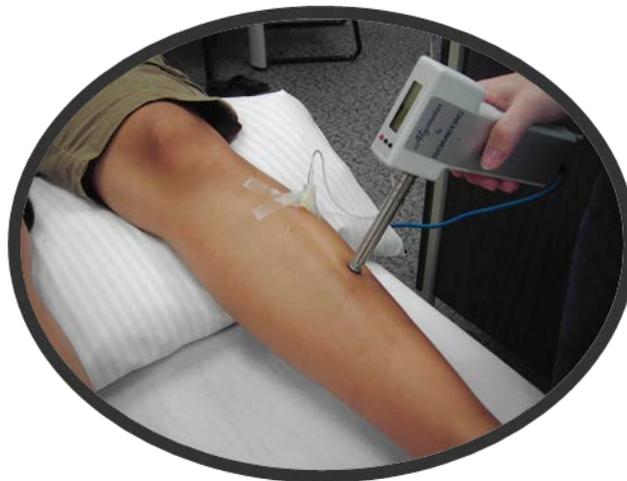


Figure 1: A patient undergoing acidic phosphate buffer (pH 5.4) infusion and measurement of pressure pain thresholds (PPTs).

Results

All participants completed the study. No complications occurred during the study and heart rate did not vary during any of the infusions. Patient 1 reported resting vulvar pain at the time of the study (2/10 rating), while Patients 2 and 3 had zero pain prior to the infusion.

Experimental pain responses are provided in Table 1. Pain was zero prior to starting the infusion; pain ratings are reported as the difference/ change from baseline. Patient 1 had no referred pain and a lower peak local pain rating (2.5) than healthy controls, placing her below average (20th and 33rd percentiles, respectively) relative to healthy women.

However, peak local pain was higher in Patients 2 and 3 (9.5 and 4.0, respectively) than the average observed in the 34 controls, placing them above 99 and 68 percent of healthy women, respectively, for this local pain response. Peak referred pain was also higher in the same two subjects (7.5 and 4.25, respectively) than the average of

the healthy age- and sex-matched controls, resulting in 100th and 94th percentile ranks. Similarly, the vulvar pain patients all exhibited greater mechanical pain sensitivity as evidenced by lower average PPT values than the average of the healthy controls, with percentile ranks from 79th to 100th.

Table 1. Absolute and percentile pain responses for each individual patient and means (SD) for healthy controls.

	Patient 1	Patient 2	Patient 3	Healthy Controls (N=34)
Resting Vulvar pain	2	0	0	-
Local Infusion Pain (0 – 10 scale)	2.5	9.5	4.0	3.0 (2.2)
percentile	32.5%	99.8%	67.5%	-
Referred pain (ankle, 0- 10)	0	7.5	4.25	1.5 (1.8)
percentile	20.2%	99.9%	93.7%	-
PPTs (kPa)	225	140	343	431 (109)
percentile	97.0%	99.6%	79.0%	-

* PPT = pressure pain threshold at 30 kPa/sec, 1 cm² tip (average of all locations).

Discussion

This is one of the first studies to examine exogenous pain model sensitivity in this patient population. We found in two of three patients, higher than average local and referred pain sensitivity, as well as elevated pressure pain sensitivity (lowered thresholds) in all three patients relative to healthy age- and sex-matched controls. The findings of decreased pressure pain thresholds in all of the subjects with vestibulodynia support the theory that women with vestibulodynia may exhibit greater generalized pain sensitivity to noxious stimuli than the general population of women. Further the large range in experimental pain responses observed in only three patients, suggests the potential for substantial heterogeneity in pain processing in this patient population.

While this is a small pilot investigation that cannot be generalized to the population as a whole, this data is congruent with other studies on this topic, suggesting that peripheral and central nervous system sensitization is likely involved in the initiation or maintenance of this chronic pain condition. Reed, et al., assessed differences in vulvar and peripheral sensitivity and similarly found women with vulvodynia were more sensitive to pressure and electrical stimuli than were control women at the vulva and at the thumb.¹⁵ Foster, et al., compared the response to intradermal capsaicin at the forearm and foot of women with vestibulodynia to controls, and found that patients with vestibulodynia demonstrated altered pain processing extending to regions far beyond the vulva.⁴ Hampson, et al., found augmented brain activation on fMRI studies in women with vulvodynia

compared to controls during local and remote (thumb) pressure evoked pain.¹² These alterations in pain sensitivity were more analogous to irritable bowel syndrome and fibromyalgia syndrome than to site-specific pain perceptions found in, for example, post herpetic neuralgia or rheumatoid arthritis, consistent with central sensitization.^{4,12}

Interestingly, resting vulvar pain was not predictive of greater pain sensitivity or referred pain to the ankle, as evidenced by Patient 1. One theory to explain this is the involvement of descending inhibitory pain pathways during a period of baseline vulvar pain. That is, the “pain inhibits pain” phenomenon or conditioned pain modulation, where pain activates descending inhibitory pathways. These pathways arise in multiple areas of the cerebrum and brainstem and inhibit transmission of nociceptive inputs at the level of the dorsal horn.¹⁶ Obviously, it is difficult to draw conclusions with a sample size of one and this patient could very well be an outlier, or simply be evidence that baseline pain is not predictive of evoked pain sensitivity.

Our findings of increased pressure pain thresholds outside the vulva region and referred pain, a form of central sensitization, in this small pilot study may further suggest the involvement of centrally-mediated pain mechanisms. This supports the hypothesis that treatment may be more efficacious if targeted to systemic rather than local therapies as well as using combination therapies to act on two or more pain pathways (peripheral sensitization, central sensitization, and pain inhibitory pathways). Continued research is needed to examine the underlying

mechanisms of vestibulodynia and develop new therapies to augment the options in current use.

This study was IRB approved by the University of Iowa.

Patient permission for the anonymous image was obtained and is maintained by the author.

This study was presented at the International Society for the Study of Vulvovaginal Disease XXIII World Congress, July 2015, New York, NY.

This work was funded in part by a grant from the National Institutes of Health, HIAMS K01 AR056134 (Dr. Frey Law).

References

1. Snyder CR, Berg C, Woodward JT, Gum A, Rand KL, Wroblewski KK, Brown J, Hackman A. Hope against the cold: individual differences in trait hope and acute pain tolerance on the cold pressor task. *J Pers.* 2005 Apr;73(2):287-312. <https://doi.org/10.1111/j.1467-6494.2005.00318.x> PubMed PMID: 15745432.
2. Mense S. Nociception from skeletal muscle in relation to clinical muscle pain. *Pain.* 1993 Sep;54(3):241-89. [https://doi.org/10.1016/0304-3959\(93\)90027-M](https://doi.org/10.1016/0304-3959(93)90027-M) PubMed PMID: 8233542.
3. Ferracuti S, De Carolis A. Relationships among Eysenck's extraversion, Rorschach's Erlebnistypus, and tolerance of experimental tonic pain (Cold Water Pressor Test). *Percept Mot Skills.* 2005 Feb;100(1):237-48. <https://doi.org/10.2466/pms.100.1.237-248> PubMed PMID: 15773714.

4. Foster DC, Dworkin RH, Wood RW. Effects of intradermal foot and forearm capsaicin injections in normal and vulvodynia-afflicted women. *Pain*. 2005 Sep;117(1-2):128-36.
<https://doi.org/10.1016/j.pain.2005.05.025> PubMed PMID: 16087295.
5. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. *Pain*. 2011 Mar;152(3 Suppl):S2-15.
<https://doi.org/10.1016/j.pain.2010.09.030> PubMed PMID: 20961685; PubMed Central PMCID: PMC3268359.
6. Graven-Nielsen T, Arendt-Nielsen L. Peripheral and central sensitization in musculoskeletal pain disorders: an experimental approach. *Curr Rheumatol Rep*. 2002 Aug;4(4):313-21.
<https://doi.org/10.1007/s11926-002-0040-y> PubMed PMID: 12126583.
7. Graven-Nielsen T, Arendt-Nielsen L. Induction and assessment of muscle pain, referred pain, and muscular hyperalgesia. *Curr Pain Headache Rep*. 2003 Dec;7(6):443-51.
<https://doi.org/10.1007/s11916-003-0060-y> PubMed PMID: 14604503.
8. Frey Law LA, Sluka KA, McMullen T, Lee J, Arendt-Nielsen L, Graven-Nielsen T. Acidic buffer induced muscle pain evokes referred pain and mechanical hyperalgesia in humans. *Pain*. 2008 Nov 30;140(2):254-64.
<https://doi.org/10.1016/j.pain.2008.08.014> PubMed PMID: 18835099; PubMed Central PMCID: PMC2613646.
9. Sluka KA, Kalra A, Moore SA. Unilateral intramuscular injections of acidic saline produce a bilateral, long-lasting hyperalgesia. *Muscle Nerve*. 2001 Jan;24(1):37-46.
[https://doi.org/10.1002/1097-4598\(200101\)24:1<37::AID-MUS4>3.0.CO;2-8](https://doi.org/10.1002/1097-4598(200101)24:1<37::AID-MUS4>3.0.CO;2-8) PubMed PMID: 11150964.
10. Bornstein J, Goldstein AT, Stockdale CK, Bergeron S, Pukall C, Zolnoun D, Coady D; consensus vulvar pain terminology committee of the International Society for the Study of Vulvovaginal Disease (ISSVD), the International Society for the Study of Women's Sexual Health (ISSWSH), and the International Pelvic Pain Society (IPPS).. 2015 ISSVD, ISSWSH and IPPS Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia. *Obstet Gynecol*. 2016 Apr;127(4):745-51.
<https://doi.org/10.1097/AOG.0000000000001359> PubMed PMID: 27008217.
11. Stockdale CK, Lawson HW. 2013 Vulvodynia Guideline update. *J Low Genit Tract Dis*. 2014 Apr;18(2):93-100.
<https://doi.org/10.1097/LGT.0000000000000021> PubMed PMID: 24633161.
12. Hampson JP, Reed BD, Clauw DJ, Bhavsar R, Gracely RH, Haefner HK, Harris RE. Augmented central pain processing in vulvodynia. *J Pain*. 2013 Jun;14(6):579-89.
<https://doi.org/10.1016/j.jpain.2013.01.767> PubMed PMID: 23578957; PubMed Central PMCID: PMC3672331.
13. Falsetta ML, Foster DC, Bonham AD, Phipps RP. A review of the available clinical therapies for vulvodynia management and new data implicating proinflammatory mediators in pain elicitation. *BJOG*. 2016 Jun 17.
<https://doi.org/10.1111/1471-0528.14157> [Epub ahead of print] PubMed PMID: 27312009.
14. Farmer MA, Maykut CA, Huberman JS, Huang L, Khalifé S, Binik YM, Apkarian AV, Schweinhardt P. Psychophysical properties of female genital sensation. *Pain*. 2013 Nov;154(11):2277-86.
<https://doi.org/10.1016/j.pain.2013.05.028> PubMed PMID: 23707679.

15. Reed BD, Sen A, Harlow SD, Haefner HK, Gracely RH. Multimodal Vulvar and Peripheral Sensitivity Among Women With Vulvodynia: A Case-Control Study. *J Low Genit Tract Dis.* 2016 Oct 7. [Epub ahead of print] <https://doi.org/10.1097/LGT.00000000000000267> PubMed PMID: 27753704.
16. Kwon M, Altin M, Duenas H, Alev L. The role of descending inhibitory pathways on chronic pain modulation and clinical implications. *Pain Pract.* 2014 Sep;14(7):656-67. <https://doi.org/10.1111/papr.12145> PubMed PMID: 24256177.