OVERNIGHT 5% LIDOCAINE THERAPY FOR TREATMENT OF VULVAR VESTIBULITIS

By

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Introduction:

Since its description some 100 years ago by Skene, vulvar vestibulitis has been an elusive disorder with poorly understood etiology, pathophysiology, and treatment [1]. After an 80 year hiatus in the literature, in 1987 Friedrich proposed the first clinical diagnostic criteria for vulvar vestibulitis: 1) Severe pain on vestibular touch and entry dyspareunia, 2) tenderness to pressure localized within the vestibule, and 3) physical findings limited to erythema of various degrees [2, 3]. The pain may be present only during attempted coitus, or may be troublesome during other daily activities. The population prevalence of vulvar vestibulitis is unknown. In a private practice setting, Goetsch reported 15% of 210 consecutively evaluated patients over 6 months met criteria for vestibulitis [4]

Despite the reported high prevalence of this disorder, randomized trials evaluating medical treatments for vulvar vestibulitis (VVS) are limited to two negative studies [25]. Nyirjesy et al reported similar response to topical Cromolyn cream (38%) vs. placebo (46%) over 3 months of therapy. Similarly, long term treatment with fluconazole, low oxalate diet and calcium produced improvement equivalent to low oxalate diet alone [5].

In 30 women treated with a series of interferon alpha-2b injections, 17 of whom had human papilloma virus (HPV) proven on biopsy, Horowitz reported clinically significant improvement in 88%. These results were not replicated by other investigators totaling 89 study participants [2, 6-9].

Several investigators have compared cognitive behavioral therapy and surgery with conflicting results. In a randomize trail involving 14 women Schultz at el showed no additional benefit of surgery above cognitive behavioral therapy alone[10]. In another randomized trial, Bergeron et al found that vestibuloplasty, cognitive-behavioral therapy, and surface electromyographic biofeedback all produced improvement at 6 months follow up, with vestibuloplasty producing the best result. He, however, cautioned against the apparent superiority of vestibuloplasty since 7 women assigned to this arm did not proceed with the treatment [11]. Bornstein et al conducted a randomized trial assessing the optimal surgical approach. He concluded that complete resection of the tissue (perineoplasty) results in full resolution of the symptoms (9/11 women) while vestibular undercutting failed to result in any improvement (10 women)[12].

In uncontrolled clinical series, the surgical approach to treatment of vulvar vestibulitis seems to have the highest reported success rate. For example, McCormack reported 80% 5-year success rate, while the review of literature by Masheb et al showed a 60-89% improvement at 6 months; 10% were worse with surgery [13, 14]. In contrast, laser treatment for VVS as an alternative to vestibuloplasty has had disappointing results; in most cases it results in worsening symptoms and poor healing [13].

Over the past five years, on the basis of clinical and histopathologic data vulvar vestibulitis has became conceptualized as a neuroinflammtory condition. [15-18]. Vulvar vestibulitis (VVS) clinically resembles post-herpetic neuralgia (PHN) in that affected

women demonstrate allodynia to touch, and respond variably to treatment, perhaps based on the severity of the nerve injury [19]. A greater than expected proportion of women with VVS also suffer from interstitial cystitis, a disorder widely held to be neuro inflammatory in nature [20, 21].

Boham-Starke's works suggests that in the case of VVS, initial nerve injury provokes sensitization of nociceptors and release of neuropeptides that maintain an inflammatory process [16, 18]. In case of PHN, subgroup with mechanical allodynia responds to prolong topical treatment with local anesthetics, Lidoderm patch®[22].

Vulvar vestibulitis is clinically similar to PHN in that it appears to have variable degrees of severity. Similar to PHN, majority of women with VVS have touch-invoked allodynia. As such, one might see a similar reduction in pain of VVS using established treatments for PHN with touch invoked allodynia. The objective of this study was to assess the response of women with VVS to treatment with prolong local anesthetics, 5% lidocaine ointment.

Material and Methods:

Between Nov. 1999 and March of 2001, all women referred to the University of North Carolina (UNC) Pelvic Pain Clinic for management of vulvar pain were evaluated for eligibility for enrollment. This study (case series) was approved by the Institutional Review Board. All patients referred for evaluation of vulvar pain underwent a standard history and physical examination. After completion of the history, they were asked to rate

their discomfort level on daily activity and intercourse using a Visual Analog Scale (VAS).

We performed comprehensive physical examinations on all women. We used cotton tipped applicator to touch labia major, labia minor and the vestibule, and we recorded presence or absence of allodynia (perception of pinprick when touched with the applicator), sensory loss, and any visible inflammatory changes.

A diagnosis of vulvar vestibulitis was made (or confirmed) using Friedrich's criteria: presence of exquisite tenderness at the vestibule, vestibular fourchette, and vestibulo-hymenal junction with or without corresponding visual changes of erythema in the absence of known pathology. A diagnosis of vulvodynia was made based on presence of daily-generalized pain/discomfort over vulva in the absence of any dermatologic or recognizable pathologic processes.

Women with dermatologic conditions (lichen sclerosis, lichen planus), chronic recurrent infectious disorders (e.g. chronic candida infections), vulvar intraepithelial neoplasia (VIN), and atrophic and ectopic dermatitis were excluded from the study unless they had concomitant VVB or vulvodynia. Women with a diagnosis of vulvar vestibulitis and generalized vulvodynia were offered the treatment. Additionally, women with clinically suspected diagnosis of vulvar vestibulitis, and generalized vulvodynia with other concomitant diagnosis (such as interstitial cystitis, vaginismus, deep dyspareunia associated with endometriosis, proctalgia fugax) were also offered the treatment. All

women with diagnosis of vulvar vestibulitis, vulvodynia, and mixed diagnosis were offered enrollment in the study.

After the diagnosis was made, study participants were instructed in the treatment procedure. Using a mirror, the anatomy of the involved area was reviewed with the patient. Patients were instructed to apply at bedtime a copious amount of 5% Xylocaine® ointment to the affected area at vestibulo-hymenal junction. Next, they were asked to place cotton ball soaked in 5% Xylocaine in the vestibule to assure constant application. Patients were instructed to use the treatment nightly, for 8 hours each night. They were also instructed to refrain from intercourse for the first 4 weeks of the treatment. A week prior to their follow-up appointment, they were instructed to resume sexual activity. During the initial phase of the study it became clear that most patients responded within 6-8 weeks of starting the therapy; hence, resumption of sexual activity was commonly delayed until at least 6 weeks of nightly therapy.

A repeat VAS score was obtained for daily activity and intercourse related discomfort in the follow up visit. Patients were also asked about the ability to have intercourse in both initial and follow up visits. Patients were reported as being able to have intercourse if they were able to tolerate intercourse during a given month, regardless of frequency or degree of discomfort. Those who were functionally celibate due to severity of symptoms were reported as not being able to have intercourse. Regardless of the patients' compliance with treatment or subsequent additional diagnoses the data for all the patients who were offered treatment was analyzed.

A combination of chart review, telephone interview and direct interview was used to obtain additional demographics on the patients. Long-term response to treatment was assessed by sending a follow up questionnaire and VAS rating a minimum of 6 months after the initiation of treatment.

The primary outcome was a change in overall and intercourse related VAS with treatment. We also assessed patients for a 'clinically significant reduction in pain' by looking at their ability to have intercourse, and a 50% reduction in intercourse related pain post treatment.

Statistical analysis was performed using STATA software (college station, TX). Univariant descriptive tabulations were followed by bivariante analysis. Paired t-tests were used to assess changes in continuous outcomes; Pearson's χ^2 and Fisher exact tests were used for categorical data.

Results:

A total of 74 patients were offered the treatment. Of the 74 patients, 2 patient declined treatment, 1 patient was spontaneously pain free within in a week of the visit and did not use the treatment, 7 patients did not show up after the first visit with no available follow up/demographic data. The reported data is based on the remaining cohort of 64 patients.

Demographic data is shown in table 1. Patients' mean age was 30±6 years, and 95% of patients had seen at least one physician with an average of 3±2 physicians in 32 months (5-216) prior to their visit to our clinics. The primary diagnosis was vestibulitis in 47 women (73%) and vulvodynia in 4 (7%) women; 13 (20%) women had the other concomitant diagnosis (vaginismus, 4; culture proven chronic recurrent yeast infection, 3; recurrent herpes,1; lichen sclerosis, 1; proctalgia fugax, 1; obsessive compulsive disorder involving genital cleansing, 1; post episiotomy perineoplasty pain, 2). The majority of the women were nulliparous. Forty-nine percent reported having had only one partner. Thirteen percent of women had a known diagnosis of endometriosis, but endometriosis was not the primary cause of dyspareunia in the majority. The majority of women had various other treatments as reported in table 2. Women who had a trial of lidocaine (before our evaluation) had used it prior to intercourse and on as needed basis.

There was no association between prior use of lidocaine and response to the treatment regimen. On average, it took 7±3 weeks of nightly therapy to see any significant improvement. A significantly higher proportion of women using the treatment reported ability to have intercourse post-treatment compared to pre-treatment, 73% vs. 40% (P=0.001). Overall, the pain rating post-treatment was 12.40 (5.20,19.58) points lower that pre-treatment pain ratings, p=0.001. Intercourse related pain score was 39.53 (30.84, 48.27) points lower post treatment, p<0.00001 (table 3).

Clinically meaningful response to treatment was defined as a 50% or more declines in pain score with treatment. Neither the number of months with symptoms, presence of endometriosis or symptom onset associated with childbirth was related to response to treatment. Women with intersitial cystitis were 6.31(1.18,32.90) less likely to respond to treatment than those without IC. Women with vulvar surgery also tended to be less likely to respond to treatment but the difference did not reach statistical significance. There was no statistically significant difference in improvement based on route of delivery or number of sexual partners. Women with other vulvar diseases were less likely than women with VS and VD to respond to treatment (p=0.009).

Forty-seven percent (30/64) of women responded to the 6 month follow up questionnaire. Women who responded to the questionnaire were 1.58(1.09-2.28) times more likely to have reported a 50% improvement on their initial treatment. On average, respondents were in treatment for 8± 5 months. Seventy percent of those responding to the follow-up assessment reported on-going use of 5% Xylocaine® ointment. Within this subset, 17% (N=5) reported nightly applications, 23% (N=7) reported application several times a week, and 27% (N =8) reported using the treatment several times a month. The mean VAS on 6 month follow up was 21±23, down 13 points from pre-treatment daily discomfort, P=0.03. Intercourse related VAS score was 31±26, down 31 points from the pretreatment value, P<0.00001.

Discussion

Most patients with post-herpetic neuralgia describe one of three types of pain: 1) spontaneous, constant burning, throbbing, aching pain; 2) intermittent sharp, stabbing, shooting, lancinating pain, which may also be spontaneous; and 3) dysesthetic pain provided by light tactile stimulation (allodynia), which usually lasts well beyond the duration of the stimulus (hyperpathia). When patients with post-herpetic neuralgia are carefully examined, the involved skin almost always shows pigment changes, scarring, and variety of sensory abnormalities (Wallace, 1997). The majority of the patients with VVS similarly complain of dysesthetic pain with few complaining of constant burning pain.

Studies of subgroups with distinct pain characteristics show different patterns of nerve injury, making post-herpetic neuralgia patients a heterogeneous population with different responses to various treatments. The three subtypes are: 1) an "irritable nociceptor" group with minimal deafferentation and touch-invoked allodynia due to peripheral nociceptor input, 2) a deafferentation group with both marked sensory loss and no allodynia, and 3) a deafferentation group with both sensory loss and allodynia due to central reorganization (Rowbotham, 1998). VVS patients appear to fall primarily into the "irritable nociceptor" group.

Bohm-Starke conducted the first study characterizing the sensory abnormalities in women with vestibulitis. He documented evidence of nociceptor sensitization signified

by diminished threshold for punctate mechanical stimulation, cold, heat, and vibratory stimuli over the posterior vestibule. Furthermore, in some women she noted evidence of somatosensory abnormalities over the anterior vestibular mucosa. Coupled with morphological studies showing proliferation of c-fibers and presence of calcitonin gene-related peptide, documented somatosensory dysfunction in VVS suggest a neuropathic process similar to what is documented in PHN. Bohm-Starke suggested that any treatment should be directed at destroying superficial nociceptor nerve endings (i.e. surgery) or reduction of neuronal hyperexcitability by ion channel blockers (something we choose to investigate, lidocaine). Lidocaine is a sodium channel blocker that prevents nerve conduction of sensory impulses. The small unmyelinated nerve fibers (C-fibers) which conduct pain, temperature, and autonomic activity are most sensitive to action of local anesthetics (Harvey, 1992). Lidocaine has a slow onset of action with moderate duration which makes it an ideal compound for chronic pain disorder such as post-herpetic neuralgia and vestibulitis. Continuous exposure to lidocaine inhibits "irritable nociceptors" and is the purported mechanism by which it provides benefit in treatment of chronic pain.

PHN patients with touch-evoked allodynia, and relatively preserved sensation often obtain marked relief from topical application of local anesthetic (Fields, 1998). Topical and injected local anesthetics have been found effective in both controlled and uncontrolled studies[23, 24]. Some patients using topical anesthetics attain sustained quiescence, whereas others many need to use treatment for many years to maintain pain relief (Galer, 1999). In this group with severe symptoms, lidocaine has been the only

treatment that significantly relieves their pain. In such patients, tolerance to lidocaine patch therapy does not occur nor do adverse events with several years of chronic daily application (Galer, 1999).

We patterned our regimen after the initial trial done by Rowbotham using 5% lidocaine under a dressing for a 12 hour period. Given the anatomic difficulty of covering the vestibular region, we began using a medication-coated cotton ball over the 8 hours of sleep. Our experience is that the cotton ball remains in place without any difficulty and is well tolerated.

The documented success of biofeedback is also consistent with the hypothesis of nociceptor hypersensitivity. Damaged c-fibers, unlike intact neurons, are not affected by sympathetic outflow (Field, 1998). After a nerve injury surviving cutaneous afferents develop noradrenergic sensitivity (Chabal, 1992). Foster et al, documented increased uretheral pressure profile in women with vestibulitis. He hypothesized that there is an additional functional component to the pain experienced with vestibulitis that is "sympathetically mediated." (Foster, 1993).

In our clinical experience, patients with interstitial cystitis invariably tend to have involvement of anterior vestibule, characterized by exquisite allodynia. Furthermore, 2 of the 6 women with IC reported numbness (these two had severe IC for many years), or limited perception of touch on the labia minora. Patients with IC were significantly less likely to respond to our treatment regimen than those without IC. We noted clinically

women with severe allodynia over the anterior vestibule tended to not respond as well to the treatment. Those with prior surgery responded favorably to the treatment as long as the area of allodynia and tenderness was limited to the posterior vestibule.

We recognize that this preliminary work is limited by several factors: the unmasked nature of the medication use, limited long term follow up, limited follow up response rate, and our patients' desire to provide a socially desirable responses. It is unlikely that the patient and physician related factors could fully explain the noted improvement in women at the most sever end of the symptom spectrum. Most of these women have suffered for a long time. Thus it is unlikely that patients' desire to provide a socially desirable outcome have a major impact on our results. Inherent limitation of this study is voluntary reliance on patients' response. Those who responded to our 6 months follow up questionnaire were more likely to have had an improvement in their symptoms. Assuming absence of any long -term benefit in non-responder the efficacy of this treatment regimen will be limited. However, we feel that even a 50% percent response rate in the severely affected population of women presents a viable alternative to a definite surgical intervention.

We are encouraged by the relatively rapid and sustained improvement among those who experienced benefit. The observed responses in women who are at the most severe end of the symptom spectrum is among many reasons that a randomized trial must be conducted to further investigate the effectiveness of this treatment regimen

Table 1. Characteristics of patient population

Women on treatment with overnight 5% Xylocaine		
Mean Years ±sd	30±6 yrs.	(n=63)
Race		
White	94%	(n=63)
Black	2%	
Others	2%	
Duration of Symptoms (months)*	32 (5-216)	(n=63)
Diagnosis		(n=64)
Vulvar vestibulitis (VS)	47(73%)	
Vulvodynia (VD)	3(5%)	
VS+VD	1(2%)	
VS+others	13(20%)	
Nulliparous	73%	(n=64)
Symptom associated with child birth	14%	(n=62)
NSVD 10%		
C/S 4%		
Endometriosis	13%	(n=60)
Interstitial cystitis	10%	(n=60)
No history of STD	87%	(n=60)
Number of sexual partners		(n=47)
1	23(49%)	
2-5	18(38%)	
5<	6 (14%)	
Number of physician seen	3±2	(n=47)

Table 2. Treatments used prior to overnight use of 5% Xylocaine®

Used Lidocaine	23(39%)	(n=59)
Used Elavil®	24(44%)	(n=55)
Used topical estrogen cream	41(69%)	(n=59)
Used Herbal remedies	12(20%)	(n=59)
TCA application	10(17%)	(n=58)
Topical steroids	32(54%)	(n=59)
Metronidazole gel	26(45%)	(n=58)
Antifungal cream	35(59%)	(n=59)
Surgical procedure for treatment ς	6(10%)	(n=63)

*Values are given as median values and ranges

ς Laser ablation, revision of episiotomy, vestibuloplasty, etc

Table 3. Result of treatment with 5% Xylocaine

	Before treatment	After treatment	
Ability to have intercourse	40%	78%	Pearson $\chi^2 = 11$; P=0.001
	Before treatment	After treatment	Mean difference (95% CI)
Overall VAS score	28.77	16.38	12.40 (5.20,19.58)*
Intercourse VAS score	75.20	35.67	39.53 (30.84,48.27) ς

*p=0.001 ς p<0.00001

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