

Early experience with topical meloxicam and lidocaine combination for the treatment of vulvodynia

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Abstract

Introduction: We report our early clinical observations on the use of topical meloxicam and lidocaine gel for patients with vulvodynia.

Methods: This is an early experience in participants with a history of vulvodynia evaluated and treated at the Queen's University Pelvic and Bladder Pain Clinic. Combination meloxicam 0.3% and lidocaine 5% were provided to the participants and they were instructed to apply 5 cc to the vulvar area twice daily. Standardized assessment was conducted for each participant before the start of the topical therapy and again at one week, and included Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), and pain scoring (Likert) for vulvar pain, in addition to a subjective global assessment after a week of treatment.

Results: Of the eight participants, six had a subjective improvement in their symptoms with the use of the combination gel. They reported between one- and four-point reductions on the Likert pain scale and mild to moderate improvement of symptoms. Common side effects reported were burning and stinging.

Conclusions: The results from this early experience are promising for a potentially effective topical treatment for vulvodynia.

Introduction

Vulvodynia, defined as a chronic idiopathic vulvar pain, remains a condition of mystery for urologists. Currently, no standardized subtypes of vulvodynia exist, but it is often described as local or generalized and primary (onset prior to sexual activity) or secondary (acquired)¹ with provoked vulvodynia (PVD) being distinguished from spontaneous vulvodynia.²

Few modalities of treatment have been empirically validated. Treatments with some proven efficacy are individual or group cognitive behavioural therapy (CBT),^{3,4} pelvic

floor physical therapy,⁵⁻⁷ and vestibulectomy.^{8,9} Medical management of vulvodynia presents a conspicuous gap in empirically validated recommendations.¹⁰ Various medical therapies, including topical (e.g., lidocaine gel or cream, comolyn cream) and systemic agents (e.g., amitriptyline, calcium citrate, desipramine, gabapentin, paroxetine, venlafaxine), have been studied in small trials and case reports.¹¹ However, large-scale, controlled trials have yet to identify an effective and safe drug management strategy for vulvodynia.

Topical agents have been gaining favour for chronic pain syndromes due to their higher local bioavailability and fewer systemic side effects, leading to greater patient adherence.¹² Numerous case series and small randomized controlled trials (RCT) suggest clinical value of various local agents for vulvodynia, including topical capsaicin,^{13,14} Botox injections,¹⁵⁻¹⁷ interferon injections,¹⁸⁻²⁰ topical estrogen,²¹ and local anesthetics (e.g., lidocaine).²²

Peripheral sensitization of nociceptors has been demonstrated as a possible mechanism of vulvodynia.²³ Such is the rationale for the use of local anesthetics, such as lidocaine, which work by blocking sodium channels in neurons, thereby increasing the threshold for depolarization.²⁴ The lidocaine 5% patch has been used to effectively treat various neuropathic pain conditions.²⁵⁻²⁷ A prospective RCT found that lidocaine and CBT significantly improved vestibular pain thresholds, quality of life scores, and sexual functioning at 12-month followup.²²

Inflammation is one of the key processes involved in vulvodynia.²⁸ Case series using combination lidocaine plus methylprednisolone²⁹ or betamethasone^{30,31} showed promising results. However, because of a lack of high-power studies for the efficacy of topical steroids and a significant side effect profile, the use of steroids is currently not recommended to treat vulvodynia.¹⁰

Non-steroidal anti-inflammatory (NSAID)-mediated analgesia is achieved by inhibition of COX-2 enzymes, thereby inhibiting prostaglandin production.³² Meloxicam is a selective COX-2 inhibitor with low molecular mass and high tissue tolerability³³ and as a result, it has a high intrinsic activity

combined with a low ulcerogenic potential; meloxicam has a therapeutic index lower than piroxicam, diclofenac, and indomethacin.³⁴⁻³⁶

Bacchav and Patravale³⁷ created a topical formulation of meloxicam demonstrating physicochemical stability, excellent *in vivo* skin penetration, and a lack of skin irritation using the Draize test. The mechanism of the topical delivery of NSAIDs is still unclear, but it is believed that local accumulation of the drug in target tissues could occur either by direct penetration or via redistribution through systemic circulation.^{38,39} It has been shown that local, targeted, subcutaneous NSAID delivery might be possible and effective through topical delivery.³⁹

We postulate that the topically applied combination meloxicam and lidocaine would synergistically reduce nociceptive thresholds in patients diagnosed with vulvodynia, resulting in symptom amelioration.

Methods

Patients

The Queen's University Pelvic/Bladder Pain Clinic evaluates patients presenting with interstitial cystitis, bladder pain syndrome, and other urological pelvic pain problems using a standardized protocol.⁴⁰ Approximately 17% of patients assessed also complain of or are diagnosed with vulvodynia. Our standard clinic approach has been to prescribe lidocaine cream locally and amitriptyline systemically, but this has led to unsatisfactory results in many patients. Based on rationale outlined in the Introduction section, we offered vulvodynia patients who have failed our standard treatment protocol a compounded combination lidocaine/meloxicam topical gel.

Intervention

Combination lidocaine 5% and meloxicam 0.3% was formulated (Chief Pharmacy, Calgary, Alberta, Canada) and provided to patients in 50 cc labeled jars. Patients were instructed to use 5 cc applied to vulvar area twice daily.

Assessments

All patients underwent standardized evaluation, which included focused history and physical examination (including pelvic examination with Q-tip test for vulvodynia); Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), as well as pain scoring (Likert) for various pain generators (including vulvar pain) were noted. Patients were assessed one week later with ICSI and ICPI, pain evaluation, and subjective global assessment (SGA). SGA was a six-point

questionnaire in which the patients described their symptoms as markedly worse, moderately worse, mildly worse, no change, mildly better, moderately better, and markedly better. Responders were defined as patients who indicated that their general symptoms were moderately or markedly better following the intervention.

Analysis

The response in terms of pain score and SGA in this early experience observational study were analyzed descriptively. Since this was not a clinical trial, no effort was made to power this analysis of pilot data based on first experience with this local combination intervention.

Results

Eight of the 10 patients offered the topical therapy applied it at least once. Seven of the eight treated patients had failed our standard vulvodynia intervention and the remaining patient had no previous treatment for vulvodynia. Of the eight participants, six had a subjective improvement in their symptoms with the use of the combination gel (Table 1). A pain score reduction between one and four were reported one week after starting the use of the topical agent. The other two participants saw a worsening of their symptoms, but they reported no change in their pain scores (Table 1). The most common side effects reported were burning and stinging.

Discussion

Most of the participants had tried recommended therapies for vulvodynia and experienced no improvement. The majority reported moderate improvement of their symptoms after a one-week trial of topical lidocaine 5% and meloxicam 0.3% combination agent. No systemic side effects were reported, corroborating the current evidence that topical agents have fewer systemic side effects.¹² Two participants discontinued use due to local adverse effects, such as burning and itching. These local side effects were likely attributable to the lidocaine^{41,42} rather than the meloxicam.⁴¹

In theory, the mechanism by which meloxicam exerts its analgesic effect is via selective COX-2 inhibition, as demonstrated in studies of systemic administration.⁴³ Meloxicam may have an additional or alternate mechanism of action when applied topically, such as inhibition of NMDA receptor hyperalgesia, as observed with topical application of diclofenac.^{44,45} If true, the combination of meloxicam and lidocaine may work synergistically on the nociceptive threshold to produce an analgesic effect.

Table 1. Early experience data

ID	Age	Symptom duration (yrs)	Associated conditions	Previous treatment(s) for vulvodynia	ICSI/ICPI pre vs. post	Pain score prior	Pain score 1 week post	Subjective global assessment	Reported side effects
1	23	4	IBS, anxiety, urethral pain	Lidocaine cream, amitriptyline	Pre: 14/13; Post: 14/13	6	5	Mildly improved	Stinging*
2	20	1	Anxiety, depression, endometriosis, persistent pelvic pain	Physiotherapy, lidocaine cream	Pre: 3/4; Post: 3/4	10	10	Moderately worse	Stinging, burning
3	43	8	IBS, urethral pain, endometriosis, dyspareunia, chronic yeast infection	Amitriptyline, anti-histamine	Pre: 15/16; Post: 19/16	8	4	Moderately improved	Stinging*, burning*
4	72	19	Dyspareunia, IBS, depression, fibromyalgia, vaginal atrophy	Tramacet, physiotherapy, lyrica, premarin	Pre: 11/4; Post: NC	9	6	Moderately improved	Itching*
5	69	2	IBS, dyspareunia, urethral pain	Amitriptyline	Pre: NC; Post: NC	7	4	Moderately improved	Numbness*
6	45	2	Dyspareunia, chronic constipation, anxiety	None	Pre: 17/13; Post: NC	8	8	Moderately worse	Stinging, burning, labia swelling
7	54	10	Vaginal atrophy, urethral pain	Lidocaine cream, premarin, amitriptyline	Pre: 14/13; Post: NC	8	6	Mildly improved	Itching*
8	35	1	Traumatic birth	Physiotherapy, lidocaine cream, PF	Pre: 14/11; Post: 11/10	8	6	Mildly improved	No issues

*Side effects only experienced during first few applications and resolved by one week assessment. IBS: irritable bowel syndrome; ICSI: Interstitial Cystitis Symptom Index; ICPI: Interstitial Cystitis Problem Index; NC: not completed.

Conclusion

The results from this early experience are promising for a potentially effective topical treatment for vulvodynia. A properly designed randomized, placebo-controlled trial is the next step to demonstrate efficacy and characterize any adverse effects.

Competing interests: Dr. Olson has financial interests in Chief Pharmacy in Calgary, AB. Dr. Nickell has been a consultant for Astellas, Auxillium, Eli Lilly, Farr Labs, Ferring, GSK, Pfizer, Redleaf Pharma, Taris Biomedical, Tribute, and Trillium Therapeutics; a lecturer for Astellas and Eli Lilly; and has participated in clinical trials supported by Eli Lilly, GSK, J&J, Pfizer, and Taris Biomedical. The remaining authors report no competing personal or financial interests.

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