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## Cromolyn cream for recalcitrant idiopathic vulvar vestibulitis: results of a placebo controlled study

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**Objective:** Patients with chronic idiopathic vulvar vestibulitis have increased mast cells when biopsied, and cromolyn has been suggested as a treatment. The purpose of this study was to assess the efficacy of 4% cromolyn cream in women with vulvar vestibulitis.

**Methods:** A prospective, double blind, randomised, placebo controlled study was initiated at two centres. Patients with vulvar vestibulitis were assigned to apply cromolyn or placebo cream to the vestibule. Symptoms (burning, irritation) and signs (erythema, extent of erythema, tenderness) were recorded on a 0–3 scale. In the sexually active patient subgroup, dyspareunia was also evaluated.

**Results:** 13 of the 26 evaluable patients received cromolyn. Patients in the cromolyn arm were more likely to have failed therapy with amitriptyline ( $p = 0.05$ ), but the two groups were otherwise similar upon study entry. Overall, scores decreased from a median of 9 to 5 ( $p = 0.001$ ) during the study, but the level of improvement was similar between both groups. Improvement was unrelated to duration of symptoms, fluconazole use, or sexual activity. Five patients (38%) taking cromolyn and six (46%) taking placebo felt they had a 50% or greater reduction in symptoms. In the 21 sexually active patients, the total score decreased from a mean of 12 to 8 ( $p = 0.005$ ), but there was no statistically significant difference between study arms.

**Conclusions:** Cromolyn cream did not confer a significant benefit in patients with vulvar vestibulitis. The large placebo response suggests the need for large well controlled studies of other treatment modalities.

(*Sex Transm Inf* 2001;77:53–57)

Keywords: cromolyn cream; vulvar vestibulitis

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Accepted for publication  
12 October 2000

## Introduction

Idiopathic vulvar vestibulitis is a syndrome characterised by unexplained chronic vulvar pain, sexual dysfunction, and psychological disability. Although exact data regarding disease prevalence remain scarce, it is seen in as many as 15% of patients referred to tertiary care centres for evaluation of chronic vaginal symptoms.<sup>1</sup> Patients with vulvar vestibulitis may complain of varying degrees of vulvar burning, irritation, and itching in their daily activities, but the main presenting complaint is one of chronic dyspareunia with intromission. At present, the aetiology and management of this condition remain unclear. Proposed aetiologies have included previous vulvovaginal candidiasis,<sup>2</sup> hypersensitivity reactions, human papillomavirus (HPV) infection,<sup>3</sup> high levels of urinary oxalates,<sup>4</sup> and neurological dysfunction. However, controlled studies to evaluate the aetiology of this syndrome have failed to establish any definitive cause.<sup>5,6</sup> As can be expected in a situation where the cause has been attributed to such a wide variety of diseases, many treatment options, ranging from topical corticosteroid ointments to partial vestibulectomy, have been proposed for this condition. Even with surgery, a failure rate of at least 25% has been reported,<sup>7</sup> and recurrence rates beyond the 1 year mark are not available.

Ashman and Ott<sup>2</sup> proposed in 1989 that *Candida albicans* antigens cross react with certain vulvovaginal tissue antigens and may pro-

vide an explanation for a possible association of vestibulitis with a preceding yeast infection. They suggested that type I hypersensitivity results from host reactivity changes in response to second contact with an exposed antigen. Such a host response would theoretically include mast cell degranulation and release of histamine. Pyka and colleagues, using a special toluidine blue staining, found mast cells in only 21% of cases of vulvar vestibulitis.<sup>8</sup> In contrast, Chaim and colleagues,<sup>9</sup> using a Giemsa stain, found increased numbers of mast cells in 16 of 16 patients undergoing surgical intervention when compared with controls. However, their comparison group involved women undergoing surgery for a non-inflammatory condition—that is, posterior colporrhaphy, who might be expected to have fewer inflammatory cells on histology. Furthermore, these findings could be somewhat non-specific and not suggestive of an allergic response, since there was no elevation of eosinophils in either study. Nevertheless, we hypothesised that vulvar vestibulitis may represent a sequela of recurrent candidiasis or as yet unidentified infection, where the primary infection has resolved, but where the local immune changes, particularly the persistence of elevated numbers of mast, lead to the localised vestibular inflammation and pain. If mast cells do play a part in the development and perpetuation of vulvar vestibulitis syndrome and if an allergic response is involved, we further postulated that a medi-

cation which blocks mast cell degranulation, such as cromolyn sodium, may help to control symptoms.

To test this hypothesis, we performed a pilot study in 11 patients with vulvar vestibulitis, using a cream containing 4% cromolyn sodium applied three times daily for 3 months. Symptoms of irritation, burning, and itching, each graded on a 0–3 (none to severe) scale, decreased from a median of 5 to 0 ( $p = 0.0001$ ). Furthermore, in the seven sexually active patients, the total symptom score decreased from a mean of 7 to 1 ( $p = 0.0002$ ). However, this was an uncontrolled study which focused exclusively on the subjective components of patient symptoms. Therefore, to further explore our results, we undertook a prospective, randomised, double blind, placebo controlled study to further evaluate this potential new therapy for vulvar vestibulitis.

### Material and methods

The patient population consisted of women referred to either the Temple University vaginitis referral centre or the Wayne State University vaginitis clinic for the evaluation and treatment of chronic vaginal symptoms. As part of the evaluation, patients routinely give an extensive medical history, with a particular emphasis placed on their vulvovaginal symptoms. Vaginal pH measurements, microscopic examination of normal saline and 10% KOH preparations, and fungal cultures are performed at every visit to diagnose possible infections. Patients were diagnosed with vulvar vestibulitis if they met the following criteria: (1) a history of vulvar pain with tampon insertion or attempted intromission, (2) focal areas of erythema confined to the vulvar vestibule, (3) tenderness upon palpation of these areas with a cotton tipped applicator, (4) exclusion of other causes for these findings, and (5) symptoms present for 6 months or more. In patients with coexisting vulvovaginal candidiasis, we considered them to also have vulvar vestibulitis if they had been on maintenance fluconazole, 100 or 200 mg weekly, for at least a month, had negative follow up fungal cultures, yet still fulfilled the criteria for vulvar vestibulitis. The patients remained on fluconazole during the study period. Patients were also required not to be taking any other therapy for vulvar vestibulitis for at least a month before enrolment.

Patients who consented to enrol in the study were randomised to one of two arms, cromolyn 4% cream or placebo cream. Randomisation consisted of a 1:1 cromolyn:placebo scheme,

performed via a computer generated randomisation table. Cromolyn cream consisted of a 4% preparation of cromolyn powder mixed in a hydrophilic cream base (acid mantle cream, Sandoz Pharmaceuticals, East Hanover, NJ, USA); placebo consisted of acid mantle cream alone. Patients applied the assigned cream three times daily to the vestibule for 3 months. They agreed to refrain from intercourse for the first month of therapy. During the study period, they returned for periodic monthly visits to monitor their progress. At each visit, symptoms of irritation, burning, and dyspareunia (in those women who were sexually active during the study period) were each graded on a 0–3 (none to severe) scale. Furthermore, investigators assigned a 0–3 value to each of the physical signs of vestibular erythema, extent of erythema, and tenderness. Vaginal pH measurements, saline and 10% KOH microscopy were performed at each visit to exclude intervening infections. Patients and investigators were unaware of the treatment group to which patients were assigned.

A statistical analysis of the study data was performed with the EPI-INFO version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA). Data are presented as medians (plus or minus lower and upper quartiles). Categorical data were analysed for significance by means of the Mantel–Haenszel  $\chi^2$  formula. If a cell value of less than 5 was encountered, a two tailed  $p$  value was calculated with the Fisher exact test. For continuous variables, a  $p$  value was calculated with the Kruskal–Wallis H test. Statistical significance was set at  $p < 0.05$ . Before initiating the study, a power analysis revealed that an enrolment of 20 patients would have a 90% chance of detecting a difference of 4 between the median total symptom/severity scores of the two groups. The protocol was approved by the institutional review boards of each institution.

### Results

A total of 34 patients consented to participate in the study. Twenty six (77%) women were deemed evaluable; 17 were enrolled at Temple, and nine at Wayne State. Two patients who received cromolyn cream complained of stinging with application of the drug; no other adverse events were noted. Of the eight non-evaluable cases, five received placebo cream, and three were randomised to cromolyn cream. Reasons for withdrawal included persistent symptoms early on in the treatment phase in three women, culture confirmed candidiasis in three, desquamative inflammatory vaginitis in one, and self treatment with both oral trimethoprim-sulphamethoxazole and topical miconazole in one. These women were removed from any further data analysis.

There were 13 evaluable patients in each arm of the study. Table 1 summarises the demographic characteristics of the study population. Patients who were randomised to 4% cromolyn cream were similar to the placebo group with regard to age, nulliparity, duration of symptoms, status of sexual activity during the study period, history of culture confirmed

Table 1 Demographic characteristics of the study population

	4% Cromolyn cream	Placebo cream	<i>p</i> Value
Median age (years)	26 (24–45)	27 (25–49)	0.6
Nulliparous	11/13 (85%)	10/13 (77%)	1.0
Median duration of symptoms (years)	2.3 (1.5–3)	2.0 (1.5–5)	0.6
Sexually active	10/13 (77%)	11/13 (85%)	0.7
History of recurrent candidiasis	8/13 (62%)	8/13 (62%)	1.0
Fluconazole maintenance	7/13 (54%)	5/13 (39%)	0.4
Previous therapies:			
Corticosteroid ointment	10/13 (77%)	10/13 (77%)	1.0
Amitriptyline	9/13 (69%)	4/13 (31%)	0.05
Oestrogen cream	2/13 (15%)	3/13 (23%)	1.0

previous vulvovaginal candidiasis, and concomitant use of maintenance fluconazole. Both groups were also similar with regard to lack of response to either topical oestrogen or topical corticosteroid therapy. However, patients who were randomised to cromolyn cream were more likely to have failed previous therapy with amitriptyline ( $p = 0.05$ ).

Upon entry into the study, patient symptoms and signs were similar between the two groups. Initial symptoms were a median of 3 (lower and upper quartiles 1–4) out of a maximum of 6 in both the cromolyn and placebo groups. Clinical signs were a mean 6 (5–7) out of a possible 9 in each group. Entry scores were 9 (8–10) out of a maximum of 15 in the cromolyn group and 9 (7–11) in the placebo group. Following 3 months of therapy, symptoms decreased by a median of 0 (0–1), signs by 4 (2–5), and overall score by 4 (2–6) in the cromolyn group. In the placebo arm, reductions of 1 (0–2) for symptoms, 2 (1–3) for signs, and overall score by 4 (2–4) were noted. Seven of 13 women who received cromolyn cream (54%) and five of 13 (38%) placebo recipients had a 50% or greater reduction in their scores. Patients were also asked to give an overall rating of how improved they felt with therapy on a 0–100% scale. Using this measure, 5/13 (38%) patients using cromolyn and 6/13 (46%) patients using placebo described a 50% or greater reduction in their overall level of comfort. None of the observed differences were statistically significant. The results were similar when controlling for previous failure with oral amitriptyline therapy.

In an attempt to further evaluate our patient responses, results were analysed with respect to factors other than type of cream patients had received during the study period. Overall, patients in both groups improved during the study period, with an initial mean score of 9 (7–11) and a final mean score of 5 (3–8) ( $p = 0.001$ ). Responses to therapy were similar when analysing sexual activity or non-activity during the study period ( $p = 0.7$ ), prestudy duration of symptoms of less or more than 1 year ( $p = 0.4$ ), and fluconazole use or non-use ( $p = 0.3$ ).

A further analysis was performed on the subgroup of 21 women who were sexually active during the study period. Initial scores for symptoms (maximum of 9), signs and total (maximum of 18) were 5 (3–7), 6 (6–8), 11.5 (10–12) in the cromolyn group, and 6 (4–8), 6 (5–7), 12 (10–14) in the placebo group. Following treatment, reductions of 1.5 (0–3) for symptoms, 3.5 (2–5) for signs, and 5.5 (2–8) for overall score were obtained in the active treatment arm; in the placebo arm, the respective decreases were 1 (0–3), 2 (0–2), and 4 (1–6). None of the observed differences were statistically significant. In this subgroup, using the same 0–100% patient assigned improvement scale, 4/10 (40%) cromolyn and 5/11 (45%) placebo patients noted a 50% or greater reduction in their overall level of comfort ( $p = 0.11$ ). Overall in this subgroup, regardless of treatment, the total score decreased from a

median of 12 (10–13) before treatment to a median of 8 (4–11) ( $p = 0.005$ ).

## Discussion

Vulvar vestibulitis is a chronic condition which adversely affects a woman's psychological and sexual wellbeing. Women who suffer from this condition are more likely to exhibit a significantly reduced interest in intercourse, have negative feelings toward it, and as a consequence refuse a partner's sexual advances.<sup>10</sup> They are also more likely to report poor health status and a history of depression during the past year.<sup>6</sup> Although it is not a life threatening process, it is one which can adversely affect a woman's quality of life, especially when one considers that it mainly affects younger women in their reproductive years.

Many treatment options have been proposed for this condition, but they each have potentially significant side effects. The treatment of last resort, partial vestibulectomy, has a failure rate of at least 25%,<sup>7</sup> and carries with it the discomfort and risks of surgery. Because of these factors, attention has turned to medical management of the disease. Injection of interferon has been reported as a potential treatment modality,<sup>11</sup> but reported success rates have been as low as 18%.<sup>12</sup> A course of interferon involves a series of 12 injections into the vestibule over a 4 week period of time, and many of patients will complain of flu-like symptoms after each injection. Nyirjesy and Halpern<sup>13</sup> described a sequential approach which consisted of topical lignocaine (lidocaine), topical desoximetasone cream, oral low dose amitriptyline, low oxalate diet with calcium citrate pills, and interferon injections, in the treatment of 72 women with vulvar vestibulitis. Patients graduated to the next step in treatment if their symptoms failed to resolve with a particular modality. Overall, 66% responded to therapy. However, finding an effective therapy for an individual patient can be quite time consuming, and some of the medications, such as amitriptyline, produce systemic side effects such as drowsiness which may limit their use. Finally, Glazer and colleagues noted that, with biofeedback therapy of the pelvic floor musculature, 79% of patients were able to resume coitus.<sup>14</sup> The treatments require a large time commitment and, in this era of managed care, obtaining the necessary approvals for biofeedback therapy are often a formidable if not impossible task. Because the effectiveness of the above therapies have only been established through uncontrolled case series at different centres, optimal management of this condition remains controversial.

Within the context of a syndrome which may be related to previous infection and increased mast cell activity and which is refractory to many treatments, it made sense to us to attempt to use cromolyn as a possible therapy. Cromolyn sodium is a cromone complex which blocks mast cell degranulation and inhibits the release of mediators from mast cells. It is primarily used as an antiasthmatic/antiallergic medication. As a topical medication, it has

been previously reported that a 4% cromolyn cream, applied intravaginally, can prevent local and cutaneous hypersensitivity reactions to seminal fluid.<sup>15</sup> In terms of safety, cromolyn should be safer and easier to use than any of the present regimens for vulvar vestibulitis. Finally, our uncontrolled pilot study demonstrated dramatic improvements in a group of 11 women who met the diagnostic criteria for vulvar vestibulitis.

The present investigation was intended to further evaluate 4% cromolyn cream as a therapy for vulvar vestibulitis. To our knowledge, this also represents the only double blind, randomised, placebo controlled study of any therapy for this condition. The protocol attempted to quantitate both the subjective elements of patient symptoms and the more objective measurements of findings on examination so that different factors could be followed over time. As a whole, the patient group had refractory disease, with a long duration of symptoms and failures with other attempts at therapy. During the study period, patients exhibited statistically significant improvement in their symptoms and signs, as well as their own perception of wellbeing. However, we were unable to demonstrate a statistically significant benefit with cromolyn cream.

There are several potential reasons for our lack of a statistically significant result. The parameters which we followed can be subtle and difficult to quantify. Patient symptoms are subjective and can vary from day to day. Scores for findings such as erythema or tenderness can vary on their own and between observers. To mitigate against these factors, patients were generally seen by the same investigator during the study period, and both patient and investigator were unaware of treatment type. However, further refinements in our methods of measuring outcome may provide a more accurate reflection of patient response. Furthermore, it should be noted that our study was of a group of women who had failed other therapies for vulvar vestibulitis. The treatment group had somewhat more recalcitrant disease, with more failures with amitriptyline therapy, but analysis of our data when we controlled for previous amitriptyline use did not improve our results. However, by choosing to enrol patients with recalcitrant vulvar vestibulitis, we may have studied women who were less likely to respond to cromolyn cream. Finally, our study could be subject to a type II statistical error. In the initial power analysis, we had assumed that the standard deviation within both groups would be 2.5. In reality, patients in both arms of the study exhibited a wide response to therapy, and the standard deviation was 3.12 in the cromolyn group and 2.48 in the placebo arm. Furthermore, there was a greater than expected improvement in the placebo group. Had we used a different set of assumptions in our power analysis, for example a standard deviation of 3 in both groups and trying to detect a difference of mean score of 3 instead of 4 between the two groups, we would have needed a total of 46 evaluable patients.

Despite the negative findings, our study does provide other insights into this disease. Although vulvar vestibulitis is considered notoriously difficult to treat, patients exhibited significant improvement in both arms of the study. The overall improvement, especially in the placebo group, was unexpected, since it is widely believed that this chronic condition is not self limiting and does not improve with time. Some of this improvement may be attributable to the soothing effects of the acid mantle cream, but it may be attributable to other factors. As with other patients with chronic vulvar symptoms, the study patients were counselled on manoeuvres to decrease exposures to potential chemical irritants such as soaps, topical antifungal therapies, and hygiene pads. In addition, the protocol entailed monitoring for and prevention of intercurrent infections. In the case of patients with coexisting recurrent vulvovaginal candidiasis, a maintenance regimen of weekly fluconazole effectively prevented them from getting acute episodes during the study period. In the other patients, repeated vaginal pH measurements, saline and 10% KOH microscopy were performed. During the 3 month study period, four (12%) enrolled patients developed a vaginal infection. This finding suggests that intercurrent infection can be a relatively common event in women with vulvar vestibulitis and may play a part in the perpetuation of symptoms. Finally, one should not minimise the potential impact of a placebo effect, which can be as high as 30% in certain studies.<sup>16</sup>

Our study results emphasise the need for careful prospective placebo controlled studies of any therapy for vulvar vestibulitis. There are presently a wide range of treatment modalities in current use, and none of them have undergone controlled evaluations of their efficacy. Given the improvement in our placebo group, the importance of including a placebo arm in any study of therapy for vulvar vestibulitis cannot be overemphasised. Protocols should attempt to provide measurements of subjective and objective components of the patient responses. In the case of cromolyn cream, further studies should include a larger group of patients, perhaps composed of women with less refractory disease. Such a larger study might also permit a more detailed analysis of which patients are more likely to see their condition improve.

*Contributors:* PN was the primary author of the submitted manuscript. He designed the research protocol, participated in patient recruitment and evaluation, and performed data entry and analysis; JDS participated in the development of the research protocol, and was involved with patient recruitment and evaluation; MVW and DJL participated in patient recruitment and evaluation. They were also involved extensively with data collection on patients; MJS participated in initial work in the development of cromolyn cream, and assisted in protocol development; SPG compounded both study and placebo medications. He prepared the randomisation protocol for the study. He assisted in protocol development.

All authors participated fully in manuscript preparation and revision.

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