Dexamethasone solution and dexamethasone in Mucolox for the treatment of oral lichen planus: a preliminary study

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Objective. The objective of this single-center, open-label, randomized, phase II study was to evaluate the safety and efficacy of dexamethasone 0.1 mg/mL solution in Mucolox (arm A) compared with dexamethasone 0.1 mg/mL solution alone (arm B) for treatment of oral lichen planus (OLP).

Study Design. Patients with clinical OLP and visual analog scale (VAS) sensitivity scores 7 or greater were randomized to arm A or B. Reticulation/erythema/ulcer (REU) scores, VAS for sensitivity and the Chronic Oral Mucosal Diseases Questionnaire (COMDQ) were completed at the baseline and the end of treatment (4 weeks). Differences were assessed by using Wilcoxon's rank-sum test.

Results. Twenty-four patients (females n = 21; median age 64.5 years; range 45−80 years) were randomly assigned to arm A or B. Four patients were excluded. Dexamethasone with or without the addition of Mucolox was effective at reducing the REU score, but the Mucolox-containing solution was relatively more effective (6-point reduction vs 4.3-point reduction; $P < .001$). There was significant improvement in the total COMDQ score in both arms (mean change 1.8 [arm A] vs 2.5 [arm B]). There were no differences in compliance between the 2 study arms ($P = .58$).

Conclusions. Dexamethasone 0.1 mg/mL solution in Mucolox was more effective for the management of OLP compared with dexamethasone 0.1 mg/mL solution alone. Larger studies are needed to confirm these preliminary findings. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:585−590)

Oral lichen planus (OLP) is a benign, chronic, immune-mediated inflammatory condition that occurs in 1% to 2% of adults.[1,2] Topical steroid therapy is considered the first line of treatment for OLP, with current treatment regimens requiring multiple application or rinses daily.[3-6] The high frequency of applications (rinses) is, in part, because of the short contact time of the medication with the affected mucosal surfaces. Although topical steroid therapy can be successful in most cases, the treatment schedule can be challenging to maintain, and its failure may require resorting to systemic medications with worse safety profiles and requiring more intricate management. There is, therefore, considerable interest in developing new and more effective topical therapies that increase adherence time or lead to less frequent daily applications resulting in improved overall outcomes.

One approach to developing more efficacious and safer therapies is targeting drug delivery to achieve high drug concentrations locally at the site of inflammation with minimal exposure of healthy or distant tissues. Mucolox is a mucoadhesive polymer gel used in the compounding of pharmaceutical preparations for the management of diseases and conditions of the oral mucosa, including oral mucositis, and mouth ulcers.[7-9]

We hypothesized that dexamethasone solution (0.1 mg/mL) in Mucolox, when swished for 5 minutes and expectorated 3 times daily, is well tolerated and more effective compared with dexamethasone solution alone in the management of OLP. The objective of this single center, 4-week, open label, randomized, phase II study was to evaluate the tolerability and clinical effectiveness of dexamethasone 0.1 mg/mL solution in a mucoadhesive vehicle (Mucolox) for the treatment of OLP.

MATERIALS AND METHODS

Patients with a clinical diagnosis of OLP and oral symptoms scored as the worst on the visual analog scale (VAS) with sensitivity scores of 7 or greater over the week before the baseline were eligible to participate in this study. Eligible patients were screened by an oral medicine specialist in the Division of Oral

Statement of Clinical Relevance

This open-label, phase II, clinical trial study showed that dexamethasone 0.1 mg/mL solution in Mucolox was clinically more effective than dexamethasone 0.1 mg/mL solution alone in the treatment of oral lichen planus. Dexamethasone 0.1 mg/mL solution in Mucolox is safe and well tolerated when used 3 times daily for the treatment of oral lichen planus.

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Medicine and Dentistry at Brigham and Women's Hospital (BWH). This study was approved by the Partners Healthcare Institutional Review Board (ClinicalTrials.gov; No. NCT02850601).

Study design

Randomization was predetermined by a computer-generated list and coordinated by the BWH Investigational Pharmacy. Patients were assigned to 1 of 2 arms: (1) arm A: compounded dexamethasone 0.1 mg/mL solution in Mucolox; and (2) dexamethasone 0.1 mg/mL solution only (arm B). A 4-week supply was dispensed, and patients were instructed to swish 5 mL of the solution in the mouth for 5 minutes and then expectorate, 3 times a day and to avoid eating or drinking for 15 minutes after rinsing. Patients maintained a daily diary and recorded each dose, the length of time rinsing, any adverse events, and the worst sensitivity score of the day.

All patients also received a prescription for fluconazole 200 mg tablets to be taken once a week or nystatin suspension to be taken 4 times daily throughout the study as prophylactic antifungal therapy.

Clinical assessment

All investigators participated in a 1-hour training session prior the beginning of the study. Mucosal disease was measured by using the reticulation/erythema/ulceration (REU) scoring system for monitoring OLP.[10] Briefly, the oral cavity was divided into 10 sites, and the severity of each type of lesion was scored according to the presence or absence of white reticular changes (0 = absent; 1 = present) and the size of the erosions/erythema or ulcers (in cm^2) (0 = no involvement; 1−3 in increasing area of involvement). Every lesion was weighted accordingly: reticular (weighted = 1); erosive/erythematous lesions were weighted 1.5, and ulcers were weighted 2. The scores for each site were then totaled. Clinical photographs were obtained both at the initial visit and at the end of treatment.

Patients completed the 26-item Chronic Oral Mucosal Diseases Quality (COMDQ) instrument at the baseline and at the end of treatment.[11] Subjective assessment of patients' oral symptoms was obtained by using instruments from the National Institutes of Health consensus documents for oral chronic graft vs host disease, a condition that is very similar to OLP.[12] This included reports of mouth sensitivity at rest and of sensitivity with stimulation (e.g., eating) on an 11-point scale. For the primary endpoint, the worst sensitivity in the past week was used. Tolerability, compliance, and subject-reported global assessment of overall improvement were evaluated at the 4-week visit.

Study endpoints and statistical analysis

The primary endpoint was a change from the baseline to 4 weeks of treatment in each subject's subjective score of the worst sensitivity experienced in the past week (0−10). The secondary endpoints included changes in REU scores and the oral health−related quality of life COMDQ. The pretreatment to post-treatment change for each item and for all items combined was assessed within each arm by using Wilcoxon's signed-rank test. In addition, each question was dichotomized and classified as "response" if the answer was "not at all," or "slightly" to a question, such as: "How isolated do you feel as a result of this oral condition?"; pretreatment to post-treatment improvement was assessed by using McNemar's test within each arm.

The sample size was calculated on the basis of the data from Rhodus et al.[5] to ensure at least 80% power and 2-sided alpha of 0.05 in detecting a t difference of 2.0 points oral sensitivity on an 11-point scale (VAS 0−10) between arm A and arm B.[5]

To evaluate improvement in clinician-reported outcome measures for OLP, REU scores of arm A were compared with those of arm B. REU scores were summarized for each arm before and after treatment and for pretreatment to post-treatment change. The pretreatment to post-treatment changes in both arms were compared by using Wilcoxon's signed-rank test.

RESULTS

Patient characteristics

Twenty-four patients (females n = 21; 87.5%), with median age 64.5 years (range 45−80 years), were enrolled and randomly assigned to arm A or B (12 patients each). Three patients were excluded because they did not return for an end-of-treatment study visit, and 1 was excluded early because of reported mild-to-moderate stomach upset and diarrhea. A total of 8 patients received dexamethasone 0.1 mg/mL solution in Mucolox (arm A), and the 12 patients in arm B received dexamethasone 0.1 mg/mL solution only. Most patients had a previous biopsy-proven diagnosis of OLP.

OLP assessments and response analysis

At baseline, the median REU score for arm A was 12 (range 6−15.5) and for arm B was 9.25 (range 3−17.5). At the end-of-treatment study visit the median REU score for arm A was 6 (range 3−32; $P < 0.05$), and the median REU score for arm B was 5 (range 1−12; $P = 0.13$) (Figure 1). Although the treatments for both arms were effective at lowering the REU scores, arm A performed statistically significantly better (6-point reduction vs 4.3-point reduction; $P < .001$). Self-reported sensitivity was also reduced in both arms, with higher subjective improvement in arm B (arm A:

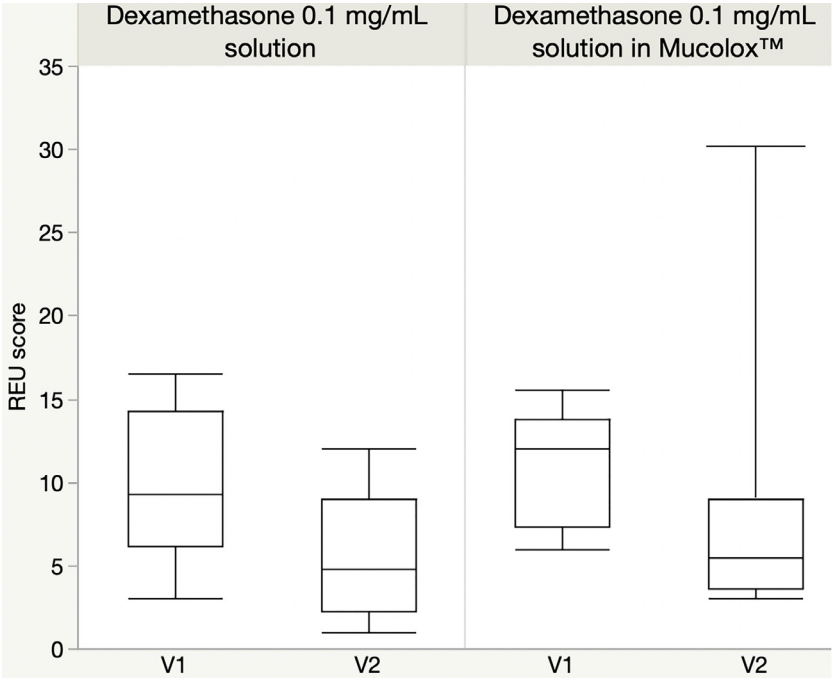

Fig. 1. Magnitude of clinical responses to dexamethasone 0.1 mg/mL solution in Mucolox (arm A) and dexamethasone 0.1 mg/mL solution (arm B). *REU,* reticulation/erythema/ulcer\. *Box:* 25th and 75th percentiles; *bars:* range (minimum and maximum values); *middle line:* median score. V1: first visit; V2: last visit.

8 [range 7−10] vs 3.5 [range 0−8]; $P < .001$; arm B: 8 [range 7−10] vs 2 [range 0−6], $P < .001$) (Figure 2).

With respect to subjects' overall self-reported responses, there were no statistically significant differences between the 2 arms ($P = .18$). Seventy-two percent of patients in arm B reported their mouths feeling "much better" (54.2%) or "moderately better" (18.2%) after 4 weeks of treatment. All patients in arm A reported

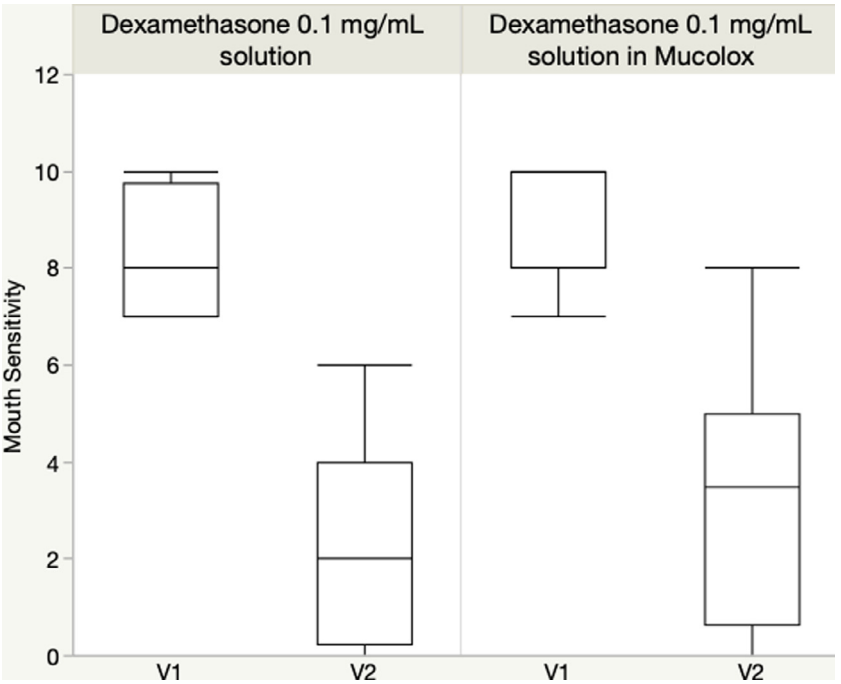

Fig. 2. Subjective responses (sensitivity) to dexamethasone 0.1 mg/mL solution in Mucolox (arm A) and dexamethasone 0.1 mg/mL solution (arm B). *Box:* 25th and 75th percentiles; *bars:* range (minimum and maximum values); *middle line:* median score. V1: first visit; V2: last visit.

Table I. Patient-reported tolerability of the therapy

Assessment	*Dexamethasone 0.1 mg/mL solution in Mucolox*	*Dexamethasone 0.1 mg/mL solution*	*P value*
Patients were asked: "Since beginning topical therapy, my mouth is:"			
About the same	0 (0.0)	1 (9.1)	.18
A little better	0 (0.0)	2 (18.2)	
Moderately better	4 (50.0)	2 (18.2)	
Much better	4 (50.0)	6 (54.5)	
Rate the level of comfort:			
No discomfort	3 (37.5)	7 (63.5)	.36
Mild discomfort	1 (12.5)	2 (18.2)	
Significant discomfort	4 (50.0)	2 (18.2)	
Rate the taste of the rinse—median (range)*	3 (0−8)	2 (0−5)	.42

*On an 11-point scale, 0−10: very pleasant to unpleasant.Data presented are n (%), unless otherwise indicated.One patient did not respond to the 3 questions.

their mouths as "moderately better" (50%) or "much better" (50%) at week 4 of treatment (Table I). Both rinses were well tolerated, with no reported differences in taste between the 2 arms ($P = .42$).

Chronic Oral Mucosal Diseases Questionnaire

The mean change for arm A in the total COMDQ score was 1.8 and that for in arm B was 2.5 (Table II). There was a higher improvement in the total COMDQ score in arm A patients compared with arm B patients (6.3 ± 1.5 vs 4.5 ± 2.5, $P < .05$; 5.9 ± 2.2 vs 3.4 ± 1.4, $P < .001$, respectively).

Compliance

Compliance data were available for all patients from review of patient diaries. Generally, compliance was good, with no differences noted between the 2 study arms ($P = .58$). Patients performed a median 84 rinses (range 71−84) in arm A and 82 rinses (range 74−84) in arm B.

DISCUSSION

In this single-center, open-label, randomized, phase II study, commercial dexamethasone 0.1 mg/mL solution compounded with Mucolox was found to be a safe option for the management of OLP when used for rinsing 3 times a day for a 5-minute swish-and-expectorate cycle. Patients receiving dexamethasone 0.1 mg/mL solution in Mucolox had a better clinical response compared with dexamethasone 0.1 mg/mL solution alone; specifically, there was a 6-point reduction vs a 4.3-point reduction ($P < .001$) of REU scores. Both arms demonstrated subjective improvement of the oral symptoms after 4 weeks of treatment.

The efficacy of dexamethasone solution in patients with OLP has been well described. Rhodus et al., in a prospective, controlled clinical trial of dexamethasone 0.1% solution in 13 patients with erosive−ulcerative OLP.[5] Significant subjective improvement in symptoms on VAS at 6 weeks (pretreatment VAS: 6.7 ± 1.4; post-treatment VAS: 2.3 ± 0.6). Hambly et al. conducted a single-blind, crossover pilot trial in 9 patients to compare the efficacy of compounded dexamethasone 0.5 mg/2 mL solution or one 0.5 mg tablet crushed and mixed with 20 mL water 3 times per day for 3 weeks for OLP.[13] All patients were instructed to rinse and hold the medication in their mouths for at least 2 to 3 minutes and then expectorate. Participants were evaluated at weeks 0, 3, 4, and 7. Compounded dexamethasone solution was found to be more effective compared with dissolved 0.5 mg dexamethasone tablet in terms of compliance, patient-perceived onset of action, and improved symptom relief.

All studies showed that to be effective, multiple applications with dexamethasone solution are needed

Table II. Chronic Oral Mucosal Diseases Questionnaire (COMDQ)

	Scale	*Dexamethasone 0.1 mg/mL solution in Mucolox (mean ± SD)*	*Dexamethasone 0.1 mg/mL solution (mean ± SD)*	*P value*
V1	Pain and function limitation	2.2 ± 0.8	2.5 ± 1.6	.45
	Medical and treatment	1.9 ± 0.8	1.5 ± 0.6	
	Social and emotional	1.7 ± 0.6	1.4 ± 0.8	
	Patient support	2.0 ± 0.7	1.9 ± 0.8	
	Total score	6.3 ± 1.5	5.9 ± 2.2	
		$< .05$	$< .001$	
V2	Pain and function limitation	1.4 ± 1.1	0.9 ± 0.6	.08
	Medical and treatment	1.7 ± 1.1	1.3 ± 0.5	
	Social and emotional	0.9 ± 0.6	0.8 ± 0.5	
	Patient support	1.8 ± 1.0	1.9 ± 0.9	
	Total score	4.5 ± 2.5	3.4 ± 1.4	

SD, standard deviation; V1, first visit; V2, last visit; P value (V1 vs. V2): $p < 0.001$.

and for several minutes. There is, therefore, considerable interest in developing new and more effective therapies that require less frequent applications. The possibility of having a treatment agent that is safe, easy to use, and cost effective, with potentially greater efficacy than the current standard of care available (e.g., steroid solutions), is ideal. Previous studies have shown that topical steroid gels or other immunosuppressive agents used in combination with Orabase for the management of OLP may increase the efficacy of the drug by increasing the contact time with the lesions.[14-16] However, no studies have looked into vehicles for drug delivery for oral solutions. Mucolox, when used as a vehicle to deliver topical dexamethasone to the oral mucosa, has the potential to effectively prolong contact time between the medication and the mucosa, leading to improved clinical outcomes because of less frequent applications needed. As shown by our findings, this technology may efficiently achieve high drug concentrations locally. Reduced frequency of applications and shorter time of topical therapy can lead to improved subject compliance, and this may translate to greater therapeutic benefit. Of note, if greater local absorption is achieved with Mucolox, careful monitoring of patients may be necessary for possible systemic absorption. However, adrenal suppression from superpotent topical steroids in the treatment of chronic dermatologic disorders is uncommon, even in long-term oral application of topical corticosteroids, such as fluocinonide and clobetasol.[17-19]

This study had several limitations. First, because of lack of blinding, there was potential for both investigator and patient bias. Second, the sample size was relatively small, and the length of the study was only 1 month; as such, conclusions regarding the efficacy of dexamethasone 0.1 mg/mL solution in Mucolox may be limited by the modest sample size, and responses to therapy may vary, depending on the length of treatment. Finally, no placebo arm was present, and this may have played a role, especially when subjective symptoms were reported.

CONCLUSIONS

Our study provided important data on the high efficacy of topical steroid therapy when combined with a carrier and delivery system, such as Mucolox, for controlling the signs and symptoms of OLP. Dexamethasone 0.1 mg/mL solution in Mucolox was clinically effective in reducing erythema, decreasing ulcerations, and improving the overall severity of the disease over the length of the study. However, larger studies are needed to confirm these preliminary findings and fully assess the efficacy and safety of a Mucolox-supplemented topical steroid rinse and compare it with that of the current Mucolox-free approach.

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