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Miconazole as adjuvant therapy for oral lichen planus: a double-blind randomized controlled trial

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Conflicts of interest
None declared.

Summary

Background Topical steroids are the first choice for the treatment of oral lichen planus (OLP). Antifungal drugs are often employed together with them, to prevent secondary oral candidosis, although it has been suggested anecdotally that they can also be beneficial for OLP itself.

Objectives To compare the effect of clobetasol propionate with and without a topical antifungal drug (miconazole) on the symptoms and extension of OLP.

Methods A randomized, parallel, double-blind trial was conducted at the Unit of Oral Medicine and Pathology of the University of Milan. Thirty-five outpatients with histologically proven OLP were randomly assigned to receive either clobetasol propionate and miconazole, or clobetasol propionate and placebo for 6 weeks. Primary outcomes included symptoms and extension of lesions; adverse effects were also recorded.

Results All the patients who concluded the study (30 of 35) showed clinical and subjective improvement within 3 weeks. The addition of miconazole did not affect in a significant way the signs and symptoms of OLP. No cases of clinical candidosis were seen in the patients taking miconazole, while one-third (five of 15) of the placebo group were affected.

Conclusions Although effective in preventing iatrogenic candidosis, the addition of miconazole to topical steroid treatment does not improve the efficacy of the therapy.

Oral lichen planus (OLP) is a chronic inflammatory condition affecting the oral mucous membranes of 0·1–4% of the population.[1] OLP is often asymptomatic, but in some patients, mainly those affected by the atrophic-erosive form, can cause symptoms ranging from burning sensation to severe pain, sometimes interfering with speaking, eating and swallowing.[1,2] Because the precise aetiological agents of this condition remain unknown, the treatment of OLP is focused mainly on reducing symptoms, through modulation of local immune response. To this aim topical corticosteroids are considered the first-choice drugs and good evidence indicates that among them clobetasol propionate is probably the most effective.[3,4] Second-choice drugs, to be employed in unresponding cases, include systemic steroids,[5] aminosalicylates,[6] retinoids[7] and local immunomodulating agents, such as ciclosporin[8,9] or the newly available tacrolimus[10] or pimecrolimus.[11]

To prevent oral candidosis, a consequence of local immunosuppressive drugs, an antifungal drug is often associated with topical corticosteroids;[3] however, no sound data are available on the frequency of such adverse effects. In addition, it is not known whether topical antifungal drugs, besides preventing oral candidosis, can also improve the efficacy of steroidal treatment, in terms of clinical outcomes such as symptoms or extension of the lesion.[12,13]

The aim of this randomized clinical trial was to compare the efficacy of topically applied clobetasol propionate with and without a topical antifungal drug (miconazole) in the treatment of patients with symptomatic OLP.

Patients and methods

Setting and participants

The study was conducted at the Oral Medicine Unit of the Dental School of the Università degli Studi di Milano (Italy), a unit accessible by patients both directly and by referral from dental or medical practitioners. Eligible patients had to meet the following criteria: (i) clinical and histological diagnosis of OLP; (ii) symptomatic form of the disease; and (iii) age over

18 years. Subjects were excluded from the study in the case of (i) previous treatment for OLP; (ii) systemic or local treatment with antifungal or corticosteroids in the 6 months prior to the study; (iii) hypersensitivity to clobetasol propionate or miconazole; or (iv) uncontrolled diabetes or hypertension, systemic conditions that could hamper participation and compliance with the study.

Randomization

Every new patient seen at the Oral Medicine Unit who met the eligibility criteria was asked to enter the trial. After being informed about the scope and methods of the study, the subjects who accepted signed the written informed consent form, and then were randomly allocated to one of the two arms of the study (test group or control group). The random allocation sequence was generated using software available online at http://graphpad.com/quickcalcs/randomize1.cfm (accessed 26 January 2007). To guarantee the allocation concealment, the sequence was hidden from the researchers determining patient eligibility, and assignment to one of the two arms was performed by a researcher who was not involved in enrolment.

Interventions, outcomes and blinding

Following randomization, two 30-mL syringes were given to every patient. One, labelled with the letter A, contained clobetasol propionate gel, the other labelled with the letter B, contained miconazole 2% gel (test group) or placebo (control group). Neither the patient nor the clinician was aware of the content of the syringes marked with the letter B, which were indistinguishable (double-blind design).

The clobetasol propionate gel was prepared by one of the authors (D.D.B.) in the hospital pharmacy, following the indications of Good Manufacturing Practice [Food and Drug Administration, U.S.A.; http://www.fda.gov/cdrh/devadvice/32.html (accessed 1 February 2007)] and the Italian pharmacopoeia, according to the following recipe: 0·5 g clobetasol propionate, 40 g hydroxyethyl cellulose, 20 mL alcohol (96 °C), 934 mL water, 20 mL methyl-parahydroxi-benzoate alcohol solution [prepared with 20 mL of alcohol (96 °C) and 2 g methyl-parahydroxi-benzoate]. As antifungal gel, a commercially available miconazole 2% preparation (Micotef oral gel; Teofarma, Valle Salimbene, Pavia, Italy) was employed. The placebo was prepared as an inactive gel.

To make use more convenient and assuring blindness, the gels were put into syringes with a screw plug.

Patients were instructed to apply the gel from syringe A (clobetasol propionate) twice daily and gel from syringe B (miconazole or placebo) once daily. Written instructions suggested applying the gel on dry mucosae and to avoid food and drink for 1 h following application. All patients were provided with a phone number to contact one of the researchers in case of problems or to get new doses of gel.

During the first visit (t_0) and the two control visits, one after 3 weeks (t_{21}) and another after 6 weeks (t_{42}), the mouth of every patient was carefully inspected, photographed and the following variables were recorded: (i) oral symptoms, registered by means of a visual analogue scale (VAS) of 10 cm, horizontal line marked 0 (no pain) to 10 (the worst pain ever experienced); and (ii) extension of the OLP lesions, measured as a percentage on the basis of a 50 site per mouth scheme (2% for each site). During control visits (t_{21} and t_{42}) the patients were asked explicitly about the occurrence of adverse events.

To measure *Candida* carriage, mouth swills, using 10 mL sterile distilled water were collected from each patient and 1 mL was cultured on caffeic acid–ferric citrate agar [Sabouraud's dextrose agar containing chloramphenicol (10 μL L^{-1})]. After 48-h incubation at 37 °C, colony forming units (cfu) per mL of mouth swill were counted.[14] To control compliance the syringes were weighed before starting and at each control visit.

Statistical methods

Fisher's exact test or the χ^2 test were used to compare binomial variables, paired or unpaired two-tailed *t*-test for continuous variables.

Results

Patients

Forty patients who visited in the clinic of the Oral Medicine Unit of the Dental School of the Università degli Studi di Milano (Italy) because of symptomatic OLP were assessed for eligibility. Two patients were excluded because of systemic conditions, in particular uncontrolled diabetes ($n = 1$) and uncontrolled hypertension ($n = 1$), and three because we considered their symptoms too mild to need treatment. All the patients meeting the inclusion criteria agreed to participate in the study. Thirty-five patients were enrolled in the study and were randomly allocated in one of the two groups: 18 were assigned to the test group (clobetasol propionate + miconazole) and 17 to control group B (clobetasol propionate + placebo). Patient characteristics are summarized in Table 1. The characteristics of the two groups did not show statistically significant differences; only VAS was at the limit of statistical significance ($P = 0{\cdot}0518$).

Five patients did not complete the trial, three from the test group and two from the control group. Among those of the test group, two were excluded because, having finished all the gel of syringe A, instead of contacting the researchers and asking for a new dose, as recommended, suspended the treatment, and two patients did not attend control visits for personal reasons. Among those of the control group, one developed a papilloma on the tongue and asked to be excluded, and one did not attend the control visits, without informing us of the reason (Fig. 1).

	Test group (n = 18)	Control group B (n = 17)	Total (n = 35)
Female	11	13	24
Male	7	4	11
Mean age, years (SD)	60·7 (11·8)	64·9 (9·9)	62·7 (11·0)
Mean VAS (SD)	4·7 (2·3)	6·2 (2·4)	5·4 (2·4)
Mean lesion extension (SD), %	26·6 (3·0)	29·9 (20·1)	28·2 (17·0)
Positive *Candida* cultures	9	7	16
HCV status	4 positive 4 negative 3 unknown	5 positive 4 negative 8 unknown	9 positive 8 negative 18 unknown

HCV, hepatitis C virus; VAS, visual analogue score.

Table 1 Characteristics of the subjects enrolled in the study, following randomization in the two groups

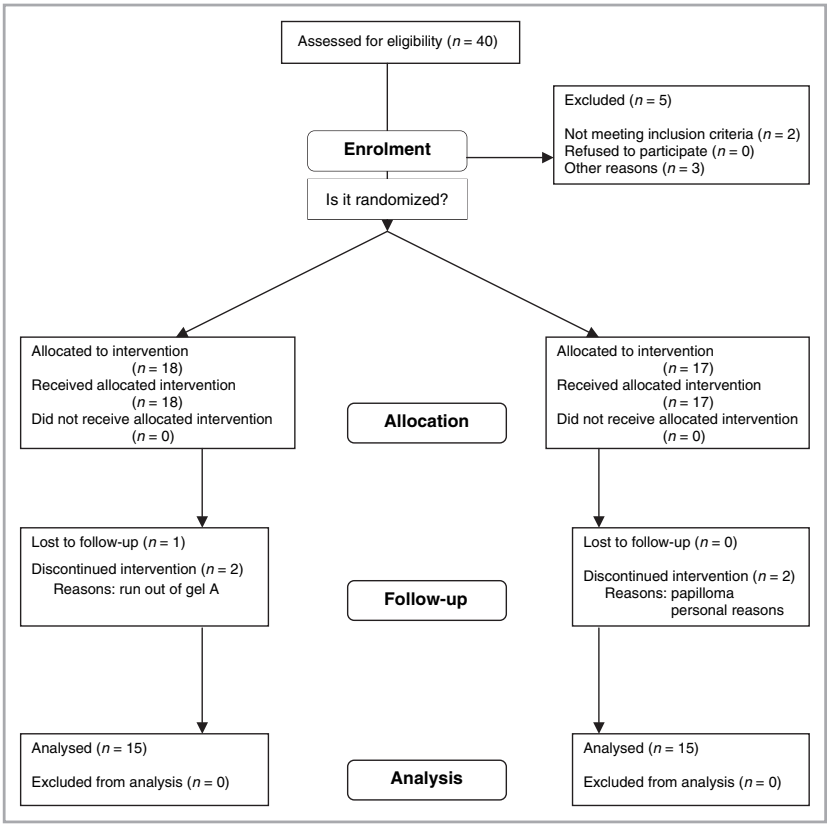

Fig 1. Flow of participants through each stage (consort flowchart).

Outcomes

At the end of the study, the two groups had used similar amounts of gel from syringe A (test group, 28·93 g; control group, 33·07 g; P = 0·4949) and syringe B (test group, 16·27 g; control group, 19·87 g; P = 0·3071). Oral symptoms improved significantly in both groups. As shown in Figure 2 the improvement was for the most part in the first 3 weeks of treatment, while in the following 3 weeks the symptoms decreased less dramatically. The statistical analysis confirmed the clinical impression (Fig. 3), in fact in both groups the comparison between pain (measured as mean VAS) at baseline and first control was highly significant (P = 0·0020 in the test group and P < 0·0001 in the control group), while between the first and second control visits the mean VAS did not change significantly (P = 0·0718 in the test group and P = 0·0833 in the control group).

Miconazole did not affect the efficacy of treatment: the comparison of mean VAS between the test and control groups

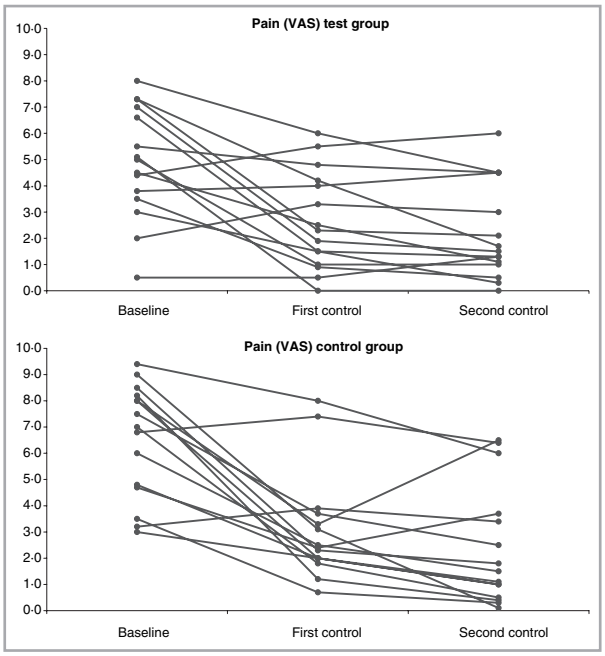

Fig 2. Modification of pain, as recorded by visual analogue scale (VAS), along the 6 weeks of treatment, in the two groups of the study.

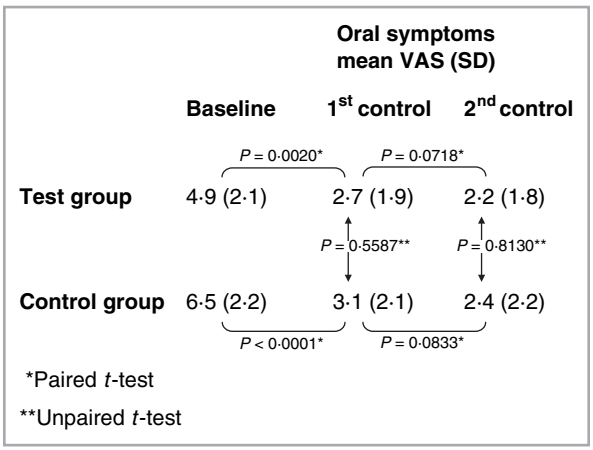

Fig 3. Comparison of the oral symptoms between the two groups and in the same group along the study. VAS, visual analogue scale.

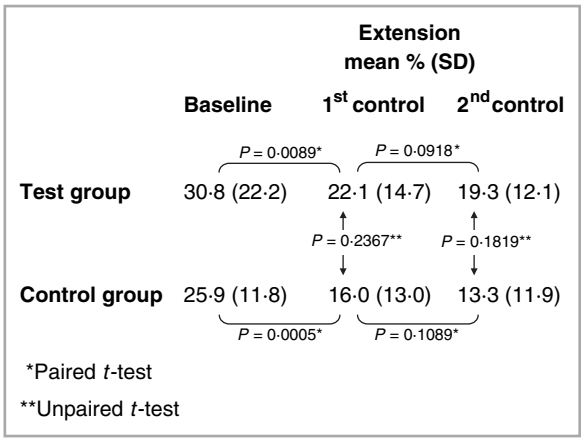

Fig 4. Comparison of the extension of the lesions between the two groups and in the same group along the study.

showed no difference, either at first (P = 0·5587) or second control visits (P = 0·0833).

Lesion extension showed similar response (Fig. 4). Both groups demonstrated a significant decrease of lesions during the first 3 weeks (P = 0·0089 in the test group and P = 0·0005 in the control group), followed by a less marked improvement in the following 3 weeks (P = 0·0918 in the test group and P = 0·1089 in the control group). Again, patients treated with clobetasol propionate and miconazole did not show better results in terms of lesion reduction; the comparison of mean extension between the test group and the control group showed no difference, either at the first (P = 0·2367) or second control visit (P = 0·1819).

Candida carriage, in terms of cfu, was similar in the two groups during the whole study (Table 2). The only notable difference was seen during the second control visit when the control group showed a higher number of patients with cfu > 100 compared with the test group (27% vs. 0%). As expected, no cases of clinical candidosis were seen in the test group, while one-third of the control group were affected during the second control visit; this difference was statistically significant by two-tailed Fisher's exact test (P = 0·0421). Four of the patients who developed candidosis had a pseudomembranous form and high cfu (three > 1000 and one = 700) at

Table 2 Comparison of *Candida* carriage and candidosis incidence between the two groups

	Test group (n = 15)			Control group (n = 15)		
	Baseline	First control	Second control	Baseline	First control	Second control
Growth/no growth[a]	9/6	5/10	7/8	7/8	8/7	7/8
cfu mL^{-1} > 100/cfu mL^{-1} < 100	1/14	0/15	5/10	0/15	4/11	5/10
Clinical signs of candidosis	0/15	0/15	0/15	0/15	0/15	5[b]/10

[a]Number of patients from whose oral cavities *Candida* spp. were isolated (growth/no growth). [b]Four pseudomembranous candidosis and one angular cheilitis.
cfu, colony-forming units.

the first control visit, the fifth developed angular cheilitis, having negative *Candida* culture throughout. To verify whether the presence of positive *Candida* carriage could predict the onset of candidosis in patients without antifungal prophylaxis, we calculated the predictive value of a positive *Candida* carriage for candidosis onset. The negative predictive value was 0·875 (95% CI 0·4735–0·9968) and positive predictive value was 0·571 (95% CI 0·1841–0·9010), meaning that in the case of negative carriage, more than 80% of patients will not develop candidosis, while in the case of a positive test, about half of the patients will develop the condition.

Discussion

In the present randomized controlled trial, we tested the hypothesis that adding an antifungal drug (miconazole) to a topical treatment with a steroid (clobetasol propionate) may improve the treatment of patients affected by symptomatic OLP. The clobetasol propionate gel showed good efficacy in the treatment of OLP. The addition of miconazole did not improve the outcomes considered, although it prevented the onset of candidosis secondary to local immunosuppression.

The beneficial effects of topical steroids for patients affected by OLP are consistent with the results documented by a number of clinical trials of different methodological quality. In particular, clobetasol propionate in aqueous solution, ointment or orabase, has been shown to be effective in comparative and placebo-controlled studies.[2] What this study adds to our knowledge on the treatment of OLP with topical steroids is that most of the beneficial effects are reached within the first 3 weeks; consequently this may be proposed as the standard duration of the initial treatment at full dosage, which may be followed by a progressive decrease of the drug until a maintenance dose is found or therapy can be suspended. It must be stressed that in the case of topical treatment, dosage refers to frequency of applications, as the amount of drug depends on the extent of lesions. Unlike other studies reporting complete remission in up to 75% of patients,[9] we did not record any such cases (i.e. complete symptomatic and clinical resolution). This may be due to the length of our study (6 weeks), which was shorter compared with similar studies, the definition of complete remission, differences in patient population, delivery system,[4] or some other unrecognized factor. At the end of the present study all patients of both groups continued topical steroid treatment with different modalities and in some cases a different drug (betamethasone mouthwash).

According to our results, the addition of an antifungal to OLP treatment with topical steroids does not improve outcomes such as pain and extension of the lesions. However, as was easily predictable, it prevented candidosis, which affected patients of the control group only. What we could not predict, as it was documented only occasionally before,[15,16] was the incidence of complications with such topical steroid treatment. Among subjects not receiving antifungal prophylaxis, candidosis developed in 30% of patients. As steroid treatment in OLP patients can last for months or years, prolonged antifungal treatment may not be indicated. On the basis of the negative predictive value of *Candida* carriage that we found (0·875 95% CI 0·4735–0·9968), it is possible to avoid antifungal prophylaxis in patients with negative *Candida* carriage before starting treatment, employing instead a local anti-infective agent with weak antifungal effect, such as a 0·12% chlorhexidine mouthwash.

In conclusion, topical clobetasol propionate gel is an effective treatment for symptomatic OLP, able to significantly improve symptoms and extension of the lesions within 3 weeks. About 30% of patients undergoing such treatment can develop oral candidosis whether or not an antifungal drug is employed; however, prophylaxis with such a drug may not be indicated in subjects with negative *Candida* carriage before starting treatment.

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