Randomized, placebo-controlled, double-blind trial of clobetasol propionate 0.05% in the treatment of oral lichen planus

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Randomized, placebo-controlled, double-blind trial of clobetasol propionate 0.05% in the treatment of oral lichen planus.

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Short title: **Clobetasol *vs* placebo in olp.**

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Abstract

OBJECTIVE: To perform a randomized, placebo-controlled, double-blind study, with a follow-up period of 6 months, for the use of topical clobetasol in cases of symptomatic oral lichen planus (OLP).

SUBJECTS AND METHODS: Thirty-two participants were analyzed, with the aims of: (I) to compare the usefulness of topically applied clobetasol propionate 0.05% (mixed with 4% hydroxyethyl cellulose gel) and 4% hydroxyethyl cellulose gel alone (considered as placebo) in the management of OLP; (II) to describe which of them is quicker in decreasing signs and reported symptoms, and (III) which is able to give the proper longer remission in the follow-up.

RESULTS: Symptoms improved in all clobetasol treated patients during the first 2 months of therapy, while only 50% of placebo control group (P=0.005) displayed similar results; of the remaining half, 12.5% did experienced a worsening whilst 37.5% remained stable. Regarding clinical signs, 87.5% of clobetasol treated patients improved, while only 62.5% of the placebo treated patients had a positive response (P=0.229).

CONCLUSIONS: It is possible to report that clobetasol, at this dosage, has been more effective than a placebo at provoking symptoms improvement in subjects affected by atrophic erosive oral lesions.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease, affecting almost 2% of the total population; female subjects are involved about more than twice than males. Patients of all ages could be affected, generally during the fifth or the sixth decades of life (Carbone *et al*, 2009b; Arduino *et al*, 2013; Baccaglini *et al*, 2013). To date, the specific etiology remains undetermined; immune dysregulation has been described to play a critical part, possibly, with the disease being the outcome of the influence of a large range of extrinsic antigens or altered self-antigens (Carbone *et al*, 2009a; Mustafa *et al*, 2015). Occasionally, precipitating aspects have been reported, including dental materials, medications, stressful events, traumatic agents, and some infectious agents (Carbone *et al*, 2009a; Baccaglini *et al*, 2013).

Two main clinical forms of OLP have been detailed: white lesions (WL) are mostly asymptomatic, while atrophic and erosive lesions (RL) could result in intense discomfort (Carbone *et al*, 2009a). It was supposed that those different clinical types may be characterized by dissimilar cells and biological events (Janardhanam *et al*, 2012); moreover, the considerable reported accumulation of CD3, CD4, CD8 and CD56 lymphocytes in the lesion, together with the consequent cell mediated immunological mechanisms, could determine the evolving of OLP into RL manifestation, with a marked tissue damage; otherwise, WL are usually characterized by less tissue damage (Lorenzini *et al*, 2013), and this response could be induced by different immune-mediated pathways.

Suggested therapies are typically symptomatic with numerous medication used, but recently, it has been published that there is unsatisfactory evidence to support the success of any specific treatment as being more reliable than another (Lodi *et al*, 2012). Management of symptomatic OLP is commonly empirical, although topical steroids are considered first line treatment, with no adequate control groups or corrected study designs (Carrozzo and Gandolfo, 1999; Zakrzewska *et al*, 2005; Arduino *et al*, 2013).

In this sense, clobetasol propionate appeared to be one of the most effective topical steroids, as in an adhesive base led to complete remission in 56-75% of patients with symptomatic OLP (Conrotto *et al*, 2006; Carbone *et al*, 2009a – 2009b; Lodi *et al*, 2012; Arduino *et al*, 2013).

To the best of our knowledge, a randomized-controlled evaluation of the efficacy of topically applied clobetasol versus placebo in the treatment of atrophic-erosive OLP is still lacking. Consequently, our aims were: (I) to compare the usefulness of topically applied clobetasol propionate 0.05% (mixed with 4% hydroxyethyl cellulose gel) and 4% hydroxyethyl cellulose gel alone (considered as placebo) in the management of OLP in a double-blind-randomized protocol, (II) to resolve which of them is quicker in decreasing signs and reported symptoms and (III) to determine which is able to give the proper remission in the follow-up.

The current trial is written according to the CONSORT statement for improving the quality of reports of randomised controlled trials (http://www.consort-statement.org/).

Subjects and method

Protocol proposal

An eight-week randomized-double-blind controlled trial was planned. Local ethical committee approval was achieved before starting and all participants were given a written informed consent; the present trial has been registered with ISRCTN (#10647973). The research was conducted in accordance with ethical principles stated in the World Medical Association Declaration of Helsinki.

Our study was split in two stages: during stage I, participants underwent topical treatment for 8 consecutive weeks, while stage II consisted of a treatment-free follow-up of six months.

Computer-generated randomization lists and allocation sequences were prepared by an independent statistician not involved in the study. Two blocks were created: for participants 1–20 and 20–50. Consequent allocation was ensured by keeping the randomization lists in the care of one of the investigators (R.B.), not involved in the clinical part of the study. The medicines were distributed in identical plastic containers, packed by an external pharmacist unaware of the protocol. The coded tubes were consecutively numbered according to the randomization list.

Subjects were divided into two groups: the first one received clobetasol propionate 0.05% cream mixed with a 4% hydroxyethyl cellulose adhesive gel, whereas the second received only the latter.

During treatment, neither the principal investigator (M.C.) nor the involved subjects knew which one of the two treatments they were using.

Participants

Consecutive individuals, attending the Oral Medicine Section of the Department of Surgical Sciences, CIR-Dental School (Turin, Italy), were enrolled, and considered eligible if having a histological diagnosis of OLP, on the basis of WHO criteria (Kramer *et al*,1978), and presenting painful lesions. Participants were not admitted if any of the succeeding exclusion conditions were reported: occurrence dysplasia in the histopathological specimen; use of lichenoid reaction inducing medication and presence of amalgam fillings nearby the lesions; interventions for OLP in the previous 12 weeks; pregnant or breastfeeding women; proved or suspected hypersensitivity to any of the chemicals used in the treatment (Arduino *et al*, 2013).

Topical formulations

1st arm: clobetasol propionate was melted in 95% alcohol with a soluble additive (Abil 8851). Hydroxyethyl cellulose was melted in boiled water and slowly turned. At the temperature of 30° C, the 4% hydroxyethyl cellulose gel was then mixed with an equivalent amount of previously melted clobetasol propionate, in order to obtain a final concentration containing 0.05% of the steroid (Carbone *et al*, 2009b).

2nd arm: 4% hydroxyethyl cellulose gel prepared as above, and then packed separately.

Intervention

The medications had to be applied twice a day for 8 consecutive weeks; for the final evaluation, we included patients with less than three missed medication doses during the entire treatment period, provided they were not consecutive (Carbone *et al*, 2009b; Arduino et al, 2013): finger rub application on dried lesions after meals without eating, drinking or speaking for at least half an hour afterwards. Anti-mycotic treatment was added to the therapy of both groups as prophylaxis against possible oropharyngeal candidosis, consisting of miconazole gel (Micotef®, LPB, Cinisello B., Milano, Italy) plus 0.12% chlorhexidine mouth rinse (Plack-out®, BYK, Gulden Italia, Cormano, Milano, Italy), once and twice daily respectively (Carbone *et al*, 2009b).

Assessment

Patient were assessed through a detailed recollection of anamnestic data and oral symptoms, followed by a conventional oral examination and photographic documentation of the lesions observed by a single physician (M.C.). This clinic-anamnestic method was done every two weeks during the protocol period, and twice during the follow-up.

The clinical data were detailed according to certain criteria (Thongprasom *et al*, 1992): score 0: no lesions; score 1: hyperkeratotic lesions; score 2: atrophic area $\leq$ 1 cm²; score

3: atrophic area > 1 cm²; score 4: erosive area ≤ 1 cm²; score 5: erosive area > 1 cm²; resolution of the clinical signs was described as before (Arduino *et al*, 2013).

Symptoms were measured using a visual analogue scale (VAS), as detailed in previous works (Conrotto *et al*, 2006; Arduino *et al*, 2013).

After the end of the protocol, the stability of the obtained results was assessed in two different times: the first after 8 weeks and the second after 24 weeks. The differences between the two groups, when present, were also evaluated. In this period, if any subject still complained symptoms or reported new ones, they would start the usual treatment, comprehensive of clobetasol propionate 0.05% mixed with 4% hydroxyethyl cellulose, as previously reported (Carbone *et al*, 2009b).

Statistical analysis

The sample size was calculated according to available data suggesting an overall efficacy of 70% and 20% for topically applied clobetasol and hydroxyetil cellulose, respectively. With a power of 85% and a type I error of 0.05, 32 patients (16 for each arm) were needed.

We described quantitative (continuous) variables using medians and first and third quartiles (Q1 and Q3); for qualitative (categorical) data, we used frequencies and percentages. The non-normality of the distributions of continuous variables were verified via Kolmogorov-Smirnov tests, so differences between medians were tested using Kruskal-Wallis tests. Fisher's exact tests were performed to evaluate differences in categorical variables.

All statistical analyses were performed using SAS-ver.9.3 (SAS Institute Inc.), and a 2-tails p-value less than 0.05 was considered statistically significant.

Results

Forty-Three Caucasian patients were screened. Four of them refused, while three did not meet our requirements and had to be excluded, with two of them being already under treatment with lichenoid reaction inducing drugs and one showing histological signs of dysplasia.

Fig. 1 reports the flow diagram for patients' recruitment.

Participants' characteristics are described in Table 1. Thirty-Six patients (30 women, 6 men, mean age 66.28) joined our study. At baseline, participants in the clobetasol group reported a median VAS of 4.00 (Q1 = 3.00; Q3 = 5.75), quite similar to that reported by subjects in the placebo group which was of 4.50 (Q1 = 3.00; Q3 = 7.00), with no statistical difference. The described score was instead worse in clobetasol group [median value of 4.00 (Q1 = 4.00; Q3 = 5.00)] when compared with that of the placebo group [median value of 4.00 (Q1 = 4.00; Q3 = 4.00)], being this difference statistical significant (Table 1).

In the first four weeks, two patients recruited in the clobetasol group dropped out for personal reasons, whereas two placebo patients gave up for uncontrolled continued pain. The remaining 32 patients were able to complete the protocol and were finally analyzed.

Table 2 describes the comparison of reported symptoms and described scores between the two groups (considering the continuous variables), during the different steps of the proposed protocol. It is worth noting that clobetasol seemed to be able to improve symptoms and signs when compared to placebo in every step of our protocol (P<0.05), except when comparing baseline data to those obtained after four weeks of treatment in terms of reported pain (P=0.237).

When considering results in terms of improvement and not in terms of continuous data, results are similar. After 4 weeks of treatment, 87.5% of the subjects in the clobetasol arm reported less pain in comparison of 40% of placebo arm, showing a faster activity for the steroid (P=0.005, with Fisher's exact test). After 8 weeks, symptoms improved in all patients treated with clobetasol (100%) during the first two months of treatment; on the

other hand, only 50% of controls undergoing therapy with placebo showed similar results (P=0.005, with Fisher's exact test) while the remaining half reported either a worsening (12.5%) or no change at all (37.5%).

Regarding clinical signs, 87.5% of clobetasol treated patients improved after 2 months of therapy, while only 62.5% of the placebo treated patients had a positive response (defined as the disappearance of all atrophic-erosive lesions, regardless of any persisting hyperkeratotic lesions); however, the difference was not statistically significant (P=0.229, Fisher's exact test).

At the end of the first eight weeks, some adverse effects were noticed; in the clobetasol group, one patient experienced episodes of gastroesophageal reflux and in the placebo group one reported a severe skin erythematous reaction (possibly due to the antimitotic medication), both enough severe to require discontinuation of therapy. Moreover, one patient in the clobetasol group described a mild increase in the fasting blood sugar level, but he was able to complete the study. There were no statistically significant differences between the two groups regarding the incidence of adverse reactions (P>0.05, Fisher's exact test).

We also assessed the reported compliance (*e.g.* number of missed application) without any difference between the two groups (data not showed). None of the enrolled subjects had specific trouble in applying the medications.

During the 24 weeks of the follow up period, six participants (37%), previously treated in the clobetasol arm, needed to be retreated due to new symptomatic oral lesions, while the remaining 10 did not experience new lesions or symptoms. At the same time, eight patients treated (50%) in the placebo arm need to be treated with the standard topical steroid therapy because of enduring symptoms. This difference was not statistically significant (P>0.05%), neither if considering the medium amount of time after the end of the protocol (22 weeks in the clobetasol arm, and 20 weeks in the placebo one).

Discussion

To the best of our knowledge, this is the first randomized, double-blind and controlled study ever reported attempting to assess efficacy of a specific topical corticosteroid (*e.g.* clobetasol propionate 0.05%) versus placebo in the topical treatment of oral erosive OLP. Clobetasol belongs to US Class I (Europe: class IV) of the corticosteroids, making it one of the most potent accessible. It is offered via a large range of classes including shampoo, mousse, ointment and emollient cream.

As previously reported by our own group either with topical steroids (Conrotto *et al*, 2006; Carbone *et al*, 2009b), or with other immunosuppressant agents (Conrotto *et al*, 2006; Arduino *et al*, 2013), we added the hydroxyethylcellulose to clobetasol, in order to make the application better attachable to the oral mucosa, and used it on its own as placebo.

Erosive OLP affecting mucosal surfaces is frequently sorer and more debilitating than the non-erosive forms. Its management is problematic and aimed at palliation rather than cure; numerous topical and systemic agents have been used with different outcomes (Cheng *et al*, 2012). At present, the treatment most commonly suggested by oral medicine physicians involves the use of corticosteroids.

In fact, topical steroids are usually considered a first-line therapy for many muco-cutaneous inflammatory conditions, being more efficient when used to treat superficial inflammation involving the epidermis, upper dermis, or dermal-epidermal junction. Topical steroid application might be superior to systemic corticosteroids for treating such conditions (Wilken *et al*, 2015).

Commonly used topical steroids include clobetasol propionate (0.025 - 0.05%), fluocinonide (0.025 - 0.05%), triamcinolone acetonide (0.05 - 0.5%), and, less frequently, fluticasone propionate or betamethasone sodium phosphate (Gupta *et al*, 2017).

Clobetasol has been widely reported to be effective in the treatment of OLP lesions through its prevention of inflammatory processes such as oedema, fibrin deposition, vasodilation, and phagocytic activity (Chamani *et al*, 2015). Furthermore, according to a very recent systematic review, topical application of 0.025 or 0.05% clobetasol propionate should be considered the first therapeutic option in the management of erosive OLP (Garcia-Pola *et al*, 2017; Gupta *et al*, 2017).

To date, only two studies performed a comparative analysis between clobetasol and placebo; our own group firstly reported this difference in a non-randomized manner, showing enhancement among 90% of OLP patients treated with clobetasol, whereas in the placebo group only 20% of subjects displayed improvement (Carbone *et al*, 1999). More recently, Brazilian Authors tried to establish a similar comparison among 22 patients with OLP-related desquamative gingivitis, finding that within the period designed to treat the gingival lesions, clobetasol propionate did not significantly outperform the placebo (Motta *et al*, 2009). However, the brief amount of time destined to treatment with such medication – only three consecutive weeks, with only one administration a day in the third week – as well as the potential protection of gingival tissues offered by trays, may have contributed to such discordance in respect to our previous results.

In the present study, clobetasol, at the aforementioned posology, has been more effective than a placebo in inducing clinical improvement amid patients affected by atrophic erosive lesions. Even though clinical signs did not show the same pattern of improvement, it is important to remember that frequently there is no positive correlation between the severity of the oral clinical pattern detectable at conventional oral examination, and the reported pain: in our clinical experience, patients with larger lesions sometimes complain less than those who deal with small but very painful lesions.

One of the limitation of the analysis is the decision to use the Thongprasom's score for the clinical assessment; this score has not been validated, differently from COMDQ for

example (Riordain *et al*, 2016), but however it has been largely used especially by our group in previous manuscripts (Thongprasom *et al*, 1992; Carbone *et al*, 1999; Conrotto *et al*, 2006; Arduino *et al*, 2014), being simply and well reproducible.

As OLP tends to relapse commonly after treatment termination, long-lasting properties and effects of used medications have to be considered carefully.

During follow-up, we observed that clobetasol participants were more stable than placebo ones, with a superior constancy of the therapeutic efficiency during the subsequent drug-free six months. Unfortunately, the usefulness of clobetasol in the long-lasting period is still poor and many patients needed to be retreated.

Concerning this matter, one study showed significant side effects after the administration of topical steroids in ulcerative and erosive lesions (Gonzalez-Moles *et al*, 2002).

However, our twenty-year clinical experience in regards to the administration of propionate clobetasol in 4% hydroxyethyl cellulose, allows us to state with enough confidence that such treatment can be considered safe, with side-effects usually limited to oral candidosis, which can be prevented through the association with topical antifungal agent and chlorhexidine-based mouthwash. In this report only one steroid treated patients (6.25%) had to stop the medication due to abdominal pain, but this type of side effects has never been reported in medical literature, and so could be defined as a very rare occurrence (less than 1 case for 10.000 treated patients); the mild hypergylcemia reported from another patient has been already described as side-effect, but usually occurring after prolonged application and high percutaneous absorption, so probably it would be difficult to explain only with topical intraoral application for 1 month (Coondoo *et al*, 2014).

Of course, we agree with the consensus among Authors that patients under this type of treatment should be supervised cautiously (Plemons *et al*, 1990; Voûte *et al*, 1993; Motta *et al*, 2009).

In conclusion, the 4% hydroxyethyl cellulose gel mixed with an equivalent amount of previously melted clobetasol propionate to obtain a finishing concentrations containing 0.05% of the drug, should be possibly considered as first line of treatment for erosive and ulcerative lesions in OLP patients, considering that the therapeutic outcome is mainly due to its corticosteroid component.

Because of the relatively small sample size, further studies with larger groups of patients and controls are needed in order to assess the reproducibility of these preliminary results.

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Conflict of interest

None to declare.

Author contributions

All the authors take responsibility for the honesty of the data and the accurateness of the data reported analysis. *Protocol design*: Arduino, Carbone and Broccoletti. *Analysis and interpretation of data*: Arduino, Campolongo, Broccoletti, Sciannameo, Ricceri. *Drafting of manuscript*: Arduino, Campolongo, Gambino, Cabras and Conrotto. *Statistical analysis*: Sciannameo, Ricceri. *Obtained funding*: Arduino and Broccoletti. *Protocol supervision*: Arduino, Carbone, Campolongo and Broccoletti.

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Figure 1 Flow of subjects through each phase.