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Original Research

Cyclosporine vs. clobetasol in the topical management of atrophic and erosive oral lichen planus

[1]Priyanka, [2]Abhishek Mukherjee, [3]Shabreen Afzal, [4]Pankaj Verma, [5]Lovleen Garg, [6]Kajal Kumari

[1]PG 3rd year, Department of Oral Medicine and Radiology, Institute of Dental Studies and Technologies, Modinagar, Uttar Pradesh, India;
[2]PG 3rd year, Department Of Oral Medicine and Radiology, DY Patil School of Dentistry, Navi Mumbai, Maharashtra, India;
[3,4]PG 3rd year, Department of Oral Pathology and Microbiology, Institute of Dental Studies and Technologies, Modinagar, Uttar Pradesh, India;
[5]PG 2nd year, Department of Oral Pathology and Microbiology, Institute of Dental Studies and Technologies, Modinagar, Uttar Pradesh, India;
[6]BDS, Madhya Pradesh Medical Science University, Jabalpur, Madhya Pradesh, India

ABSTRACT:
Background: A persistent inflammatory condition called oral lichen planus (OLP) can be unpleasant, especially in the atrophic and erosive types. Several medicines have been utilised with varied degrees of success, although the majority of treatments are empirical and lack proper study designs or suitable control groups. This study compared the efficacy of cyclosporine and clobetasol in the topical care of OLP in order to determine which is more economical and which provides the longest remission from symptoms. **Methods**: It was planned to conduct a randomised, comparative, double-blind trial. To receive either clobetasol propionate or cyclosporine for two months, forty consecutive patients were split into two groups. The 4% hydroxyethyl cellulose bioadhesive gel contained both medications. Additionally, antimycotic prophylaxis was administered. Patients got a follow-up exam two months after the completion of their therapy. **Results**: There were overall 100 subjects. There were no significant differences between the two groups with regard to age, gender, presence of hepatitis C virus (HCV) infection, or clinical and symptomatic characteristics at baseline. **Conclusions**: Although cyclosporine and clobetasol have similar effects on symptoms, clobetasol is more successful than cyclosporine at causing clinical improvement. Contrarily, clobetasol has a higher incidence of side effects than cyclosporine and provides less stable results once medication finishes. Cyclosporin is more than five times more expensive per day than clobetasol.

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Corresponding author: Priyanka, PG 3rd year, Department of Oral Medicine and Radiology, Institute of Dental Studies and Technologies, Modinagar, Uttar Pradesh, India

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INTRODUCTION

Lichen planus is a chronic inflammatory disease that affects the skin, hair follicles, nails, and mucosa.[1] Mucosal surfaces affected include the oral, genital, ocular, otic, esophageal surfaces, and in rarer instances, the bladder, nasal, laryngeal, and anal surfaces. The skin and oral mucosa are the major sites that are affected.[2] The oral variant, termed oral lichen planus (OLP), is a chronic condition with periods of relapses and remissions, requiring long-term symptomatic treatment and surveillance monitoring. About 15% of patients with oral lichen planus (OLP) develop cutaneous lesions, and 20% develop genital lesions.[3]In the oral cavity, the disease assumes somewhat different clinical appearance than on the skin, and is characterized by lesions consisting of radiating white, gray, velvety, thread-like papules in a linear, annular and retiform arrangement forming typical lacy, reticular patches, rings and streaks. A tiny white elevated dot is present at the intersection of white lines known here as striae of Wickham as compared to Wickham striae in skin.[4] The lesions are asymptomatic, bilaterally/symmetrically anywhere in the oral cavity,[5] but most common on buccal mucosa,

tongue, lips, gingiva, floor of mouth, palate and may appear weeks or months before the appearance of cutaneous lesions. Topical corticosteroids (CS) are the mainstay of therapy in OLP, but their long-term use is limited by well-known adverse events.[6,7] Moreover, not all patients respond adequately and in some cases the disease is particularly difficult to treat. Thus, topical formulations of calcineurin inhibitors were reported as alternative therapeutic options, due to their capability to inhibit T-lymphocyte proliferation and decrease proinflammatory cytokine production.[8,9,10]
Hence, this study was conducted to assess the comparison of Cyclosporine vs. clobetasol in the topical management of atrophic and erosive oral lichen planus.

MATERIAL AND METHODS

In our study, 100 consecutive white patients with a mean age of 62 years (60 women and 40 males) were enrolled. The following were the inclusion requirements. (i) Diagnosis of atrophic/erosive OLP based on clinical and histological findings in accordance with WHO guidelines. The clinical forms were distinguished by reticular keratosis plus erythema (erosive variation) or erosion ulcerations (atrophic variety) according to internationally established criteria. (ii) The existence of uncomfortable lesions. The following conditions had to be met in order to be excluded: (i) the presence of histological signs of dysplasia; (ii) the use of medications that can cause a lichenoid reaction; (iii) the presence of amalgam fillings close to lesions; (iv) treatment for OLP within the preceding six months; (v) the presence of skin, genital, or other extraoral lesions; and (vi) the presence of pregnant or nursing women. The patients underwent liver screening following the recording of their medical histories. Both cyclosporine and clobetasol propionate ointment were combined individually with 4% hydroxyethyl cellulose gel to produce final concentrations of 0025% for cyclosporine and 15% for clobetasol.30 According to Novartis, the final cyclosporine concentration was chosen. Using the same scoop, the same amount of each medication was applied twice daily for two months. To prevent a dose-related impact, the containers were weighed to determine the maximum amount of each clobetasol/cyclosporine preparation that could be used.

RESULTS

There were overall 100 subjects. There were no significant differences between the two groups with regard to age, gender, presence of hepatitis C virus (HCV) infection, or clinical and symptomatic characteristics at baseline.

Table 1: Adverse effects due to the topical treatment

Adverse effects	Clobetasol group (n=50)	Cyclosporine group (n=50)
Dyspepsia	30	10
Skin rashes	15	00
Parotid swelling	05	00

30,15 as well as 5 subjects from Clobetasol group experienced dyspepsia, skin rashes and parotid swelling. Whereas, 10 subjects from Cyclosporine group showed dyspepsia.

Table 2: Clinical response in the improved patients after 2 months of follow-up.

Clinical response	Clobetasol group (n=50)	Cyclosporine group (n=50)
Stable	03	46
Unstable	47	04
Total	50	50

Comparing the two treatment modalities, clobetasol gave significantly more side-effects than cyclosporine. Two months after the end of therapy, only 3 of the 50 clobetasol-treated patients whose clinical scores had improved were stable (6%), whereas 46 of the 50 cyclosporine-treated patients who had improved were stable (92%).
Regarding signs, 43 of the 50 clobetasol-treated patients (86%) improved after 2 months of therapy, while 33 of the 50 cyclosporine-treated patients (66%) had a positive clinical response. The difference was statistically significant. In particular, 24 clobetasol-treated patients (48%) had complete remission of atrophic /erosive lesions, whereas in the cyclosporine group the same goal was reached by 12 subjects (24%). The difference was not statistically significant.
Symptomatology improved in 45 clobetasol-treated patients (90%) and in 39 cyclosporine-treated patients (78%). Complete remission of symptomatology occurred in 14 clobetasol-treated patients (28%) and in 9 cyclosporine-treated patients (18%). Again, the difference was not statistically significant. 7 patients (14%) were HCV positive. There was no correlation between the presence of the virus and the results of the therapy, nor did OLP treatment apparently influence liver outcome as suggested by quantitative, reverse transcriptionpolymerase chain reaction-based analysis.
None of the patients developed oropharyngeal candidosis. During treatment, blood cortisol levels were stable and blood cyclosporine levels were undetectable. In the clobetasol group, three patients had dyspepsia, two had skin rashes, and one had parotid swelling possibly related to chlorhexidine. In the cyclosporine group, one patient had dyspepsia.

None of these adverse effects was severe enough to require discontinuation of therapy.

DISCUSSION

OLP is a debilitating mucosal disease which can be unresponsive to topical CS and might run a chronic course.[11] In this study, we report the outcomes of a series of 21 consecutive patients with steroid-refractory OLP, who underwent a predefined treatment regimen with low-dose CSA mouth rinse (2 mL twice daily) for four weeks followed by discontinuation of treatment for another four weeks. Pain (VAS), clinical picture (PGA) and quality of life (DLQI) were assessed at the beginning of treatment, at four weeks—when CSA therapy was discontinued—and after another four weeks without therapy. Overall, we found that four weeks of continuous topical CSA resulted in a significant reduction in pain ($p = 0.0003$), and vice versa, discontinuation of CSA led to a significant and relatively swift recurrence of pain at week eight ($p = 0.032$). The topical use of corticosteroids has been recommended as the mainstay of treatment for symptomatic OLP and various studies have analyzed the effectiveness of various formulations of topical corticosteroids of different potency.[12]

Hence, this study was conducted to assess the comparison of Cyclosporine vs. clobetasol in the topical management of atrophic and erosive oral lichen planus.

In this study, there were overall 100 subjects. There were no significant differences between the two groups with regard to age, gender, presence of hepatitis C virus (HCV) infection, or clinical and symptomatic characteristics at baseline. 30,15 as well as 5 subjects from Clobetasol group experienced dyspepsia, skin rashes and parotid swelling. Whereas, 10 subjects from Cyclosporine group showed dyspepsia. Comparing the two treatment modalities, clobetasol gave significantly more side-effects than cyclosporine. Two months after the end of therapy, only 3 of the 50 clobetasol-treated patients whose clinical scores had improved were stable (6%), whereas 46 of the 50 cyclosporine-treated patients who had improved were stable (92%).

Regarding signs, 43 of the 50 clobetasol-treated patients (86%) improved after 2 months of therapy, while 33 of the 50 cyclosporine-treated patients (66%) had a positive clinical response. The difference was statistically significant. In particular, 24 clobetasol-treated patients (48%) had complete remission of atrophic ⁄erosive lesions, whereas in the cyclosporine group the same goal was reached by 12 subjects (24%). The difference was not statistically significant.

Symptomatology improved in 45 clobetasol-treated patients (90%) and in 39 cyclosporine-treated patients (78%). Complete remission of symptomatology occurred in 14 clobetasol-treated patients (28%) and in 9 cyclosporine-treated patients (18%). Again, the difference was not statistically significant. 7 patients (14%) were HCV positive. There was no correlation between the presence of the virus and the results of the therapy, nor did OLP treatment apparently influence liver outcome as suggested by quantitative, reverse transcriptionpolymerase chain reaction-based analysis.

None of the patients developed oropharyngeal candidosis. During treatment, blood cortisol levels were stable and blood cyclosporine levels were undetectable. In the clobetasol group, three patients had dyspepsia, two had skin rashes, and one had parotid swelling possibly related to chlorhexidine. In the cyclosporine group, one patient had dyspepsia. None of these adverse effects was severe enough to require discontinuation of therapy.

D Conrotto et al[13] compared the effectiveness of clobetasol and cyclosporine in the topical management of OLP and to evaluate which is more cost-effective and which gives the longest remission from signs and symptoms. A randomized, comparative, double-blind study was designed. Forty consecutive patients were divided into two groups to receive clobetasol propionate or cyclosporine for 2 months. Both drugs were placed in 4% hydroxyethyl cellulose bioadhesive gel. Antimycotic prophylaxis was also given. After the end of therapy, patients underwent a 2-month follow-up. Eighteen of 19 clobetasol-treated patients (95%) improved after 2 months of therapy, while 13 of 20 cyclosporine-treated patients (65%) had a clinical response ($P = 0.04$). Symptomatology improved in 18 clobetasol-treated patients (95%) and in 17 cyclosporine-treated patients (85%) (not statistically significantly different). Two months after the end of therapy, 33% of clobetasol-treated patients and 77% of cyclosporine-treated patients were stable ($P = 0.04$). Clobetasol produced significantly more side-effects than cyclosporine ($P = 0.04$). The daily cost of cyclosporine treatment was 1.82 compared with 0.35 for clobetasol therapy.

Georgaki et al[14]compared the effectiveness of topical dexamethasone vs. topical cyclosporine in treatment of symptomatic OLP. Thirty-two patients with biopsy-proven symptomatic OLP were randomly assigned to two therapeutic groups: dexamethasone 2mg/5ml or cyclosporine 100mg/ml, both administered topically in a swish and spit method three times a day for 4 weeks. The patients were followed up for a total of 6 months. Assessed parameters included clinical scoring (according to Thongprasom's scale, 0-5), pain (VAS scale, 0-10), dysphagia and speech difficulties (none, mild or severe). Possible side effects, including fungal overgrowth, were also recorded. At the end of the 4-week treatment period, both dexamethasone and cyclosporine showed a statistically significant improvement in clinical scoring ($p<0.025$ and $p=0.034$, respectively), which was better with dexamethasone ($p=0.001$). In addition, both dexamethasone and cyclosporine induced statistical significant improvement in pain and dysphagia (and

speech difficulties for dexamethasone), without significant differences between the two groups. Regarding side effects, patients in the dexamethasone group developed candidiasis more frequently compared to cyclosporine (p=0.031). At the end of the 6-month follow-up period, the difference in response between the two groups was not statistically significant. Interestingly, a trend for further improvement compared with the end of the 4-week treatment period was noticed only for patients treated with cyclosporine.

CONCLUSION

Although cyclosporine and clobetasol have similar effects on symptoms, clobetasol is more successful than cyclosporine at causing clinical improvement. Contrarily, clobetasol has a higher incidence of side effects than cyclosporine and provides less stable results once medication finishes. Cyclosporin is more than five times more expensive per day than clobetasol.

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