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Original Article

Safety and efficacy of hydroxychloroquine in patients of symptomatic oral lichen planus

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Abstract

Background A wide variety of therapies have been used to treat symptomatic oral lichen planus (OLP). Role of anti-malarial agents in oral lichen planus is not fully studied.

Aim To evaluate safety and efficacy of hydroxychloroquine in the treatment of symptomatic OLP.

Methods Thirty seven patients with symptomatic OLP were included in the study. Patients were started on tablet hydroxychloroquine 200 mg twice daily and continued for a period of 6 months. Clinical evaluation was performed at the beginning of the treatment and then every 2 months during 6-month period of active treatment and thereafter again after 6 months of follow-up. Pain and clinical evaluation were done using visual analogue scale (VAS) and Thongprasom scale.

Results Thirty-seven patients were included; however, 7 patients were lost to follow-up, and excluded from final analysis. At the time of completion of therapy, 80% of the patients had no lesions. There was no recurrence until 6 months after completion of therapy. Gastritis was the most common adverse event. There were no other serious adverse events.

Conclusion Hydroxychloroquine is the effective and safe treatment for symptomatic OLP.

Key words
Oral lichen planus, hydroxychloroquine, anti-malarials.

Introduction

Lichen planus (LP) is a chronic inflammatory mucocutaneous disease that can affect the skin, mucous membranes, nails and hair follicles. Oral LP (OLP) is reported to occur in 0.5–2.2% of the population with a peak incidence in the 30–60 years age range and a female predominance of 2:1.[1] A wide variety of therapies has been used to treat symptomatic OLP. The asymptomatic forms do not warrant pharmacotherapy but are only supposed to be periodically followed up by clinicians. On the contrary, symptomatic OLP are treated with high potency topical corticosteroids, systemic prednisone or immunosuppressive agents like cyclosporine, tacrolimus and thalidomide.[2] The use of antimalarial agents in various skin diseases has been well known. Although they are not usually considered for the management of symptomatic OLP, there are studies indicating their beneficial effect in OLP.[3-7] Hydroxychloroquine (HCQ) has immunoregulatory effects, including the reduction of production of inflammatory cytokines. However, the detailed mechanism of action of these treatments on OLP is not known.[6]

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There is paucity of data on efficacy and safety of hydroxychloroquine in the treatment of symptomatic OLP; we aimed to carry out this study.

Subjects and Methods

The study was conducted at Dr. R. P. Govt. Medical College, Kangra at Tanda, Himachal Pradesh after obtaining clearance from institutional ethical committee and registration with clinical trial registry from September 2018 to September 2019, Patients clinically diagnosed with oral lichen planus and presenting consecutively in the outdoor clinic of Dermatology, Venereology & Leprosy Department were included in the study. The patients aged <18 years, with asymptomatic oral lesions, pregnant or lactating women, patients using drugs inducing lichenoid reaction, with presence of amalgam filling close to lesions, presence of skin, genital or other extra oral lesions, chronic liver disease, hematological disease and immune system dysfunction, any other absolute/relative contraindications of use of hydroxychloroquine, and/ or refusal to participate were excluded from the study.

Treatment protocol Each patient was started on tablet HCQ 200 mg twice daily and continued for a period of 6 months. Clinical evaluation was performed at the beginning of the treatment and then every 2 months during 6-month period of active treatment and thereafter again after 6 months of follow-up.

Data collection The clinical data comprised of age, gender, lesion site, medical background, and symptoms of OLP. All patients were subjected to baseline ophthalmologic examination and blood tests that included a hemogram, liver and renal functional examination, and serology for hepatitis C virus. The efficacy of treatment was evaluated according to severity of pain and burning as well as type and severity of lesion. The visual analogue scale (VAS) was used to investigate the severity of patient's symptoms. The VAS consists of a 10-cm horizontal line marked 0 (no pain) to 10 (most severe pain experienced). Atrophic and erosive changes were quantified based on the Thongprasom scale [Score 5: white striae with erosive area >1 cm^2; Score 4: white striae with erosive area <1 cm^2; Score 3: white striae with atrophic area >1 cm^2; Score 2: white striae with atrophic area <1 cm^2; Score 1: mild white striae without erythematous or erosive area, and Score 0: no lesions]

Statistical analysis Data were presented as frequency, percentages, mean, and standard deviation. Quantitative variables between 2 groups were compared using Student t-test. P value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v21.

Results

In the present study, 37 patients were included in the study. However, 7 patients were lost to follow-up; hence, these patients were excluded from final analysis.

General characteristics General characteristics of the subjects have been presented in **Table 1**. 73% of the patients aged between 31 and 60 years. 53% of the patients were females. 33% patients and 20% patients had previous history of diabetes and hypertension respectively. 10% patients were consuming alcohol while 3% were active smokers.

Laboratory investigations In the present study, 33% patients had fasting blood glucose higher than 125 mg/dl. 50% patients had blood cholesterol levels more than 200 mg/ dl. None of the patients was anti-HCV positive.

Table 1 General characteristics

	Number of Patients(%)
Age	
≤30	3(10)
31-60	22(73.3)
>60	5(16.7)
Mean±SD	46.87±12.86
Range	18-74
Sex	
Male	14(46.7)
Female	16(53.3)
Male:Female Ratio	0.87:1
Patients history	
Diabetes	10(33.3)
Hypertension	6(20)
Alcohol abuse	3(10)
Smoking	1(3.3)

Table 2 Change in VAS score with treatment

Site	*VAS Score*	*P Value*
Baseline	5.33±1.21	
2 Months	3.43±1.13	<0.00001
4 Months	1.57±1.30	<0.00001
6 Months	0.40±1.10	<0.00001
8 Months	0.37±0.99	<0.00001
10 Months	0.37±0.99	<0.00001
12 Months	0.37±0.99	<0.00001

Ophthalmic examination was normal in all the patients.

Cutaneous examination 70% lesions were present on buccal mucosa while 13.3% lesions were present on tongue. 3.3% lesions each were present on hard palate and lower lip. 10% lesions were present on more than one site **(Figure 1)**. 63.3% of the lesions were reticulate and atrophic while 36.7% of the lesions were reticulate and erosive.

Pain score In the present study, we observed a statistically significant decrease in pain score from 2 months up to 12 months when compared with baseline **(Table 2)**.

Clinical score Our study observed that at the time of completion of therapy, 80% of the patients had no lesions **(Table 3)**. We also observed no recurrence until 6 months after completion of therapy.

Adverse events Gastritis was the most common adverse event at the time of start of therapy as well after completion of therapy (80%). The other adverse events were headache and weakness in 33% and 7% patients respectively

Discussion

The present study aimed to evaluate efficacy and safety of HCQ in the treatment of symptomatic OLP. In our study, 63% of the lesions were reticulate and atrophic while the remaining were erosive. Munde *et al*. reported that reticular type of OLP was the most common form and was present in 83.5% patients.

Erosive form was observed in 15.6% patients while atrophic OLP was present in only one patient.[8]

Table 3 Clinical Score

Thongprasom scale	*White striae with erosive area >1 cm²*	*white striae with erosive area <1 cm²*	*White striae with atrophic area >1 cm²*	*White striae with atrophic area <1 cm²*	*Mild white striae without erythematous or erosive area*	*No lesions*
Score	5	4	3	2	1	0
Before treatment n(%)	1 (3.3)	9 (30)	19 (63.3)	1 (3.3)	0	0
2 Months n(%)	0	1 (3.3)	40	14 (46.7)	10	0
4 Months n(%)	0	1 (3.3)	6 (20)	2 (6.7)	16 (53.3)	5 (16.7)
6 Months n(%)	0	1 (3.3)	4 (13.3)	0	1 (3.3)	24 (80)
8 Months n(%)	0	1 (3.3)	3 (10)	1 (3.3)	1 (3.3)	24 (80)
10 Months n(%)	0	1 (3.3)	4 (13.3)		1 (3.3)	24 (80)
12 Months n(%)	0	1 (3.3)	4 (13.3)		1 (3.3)	24 (80)

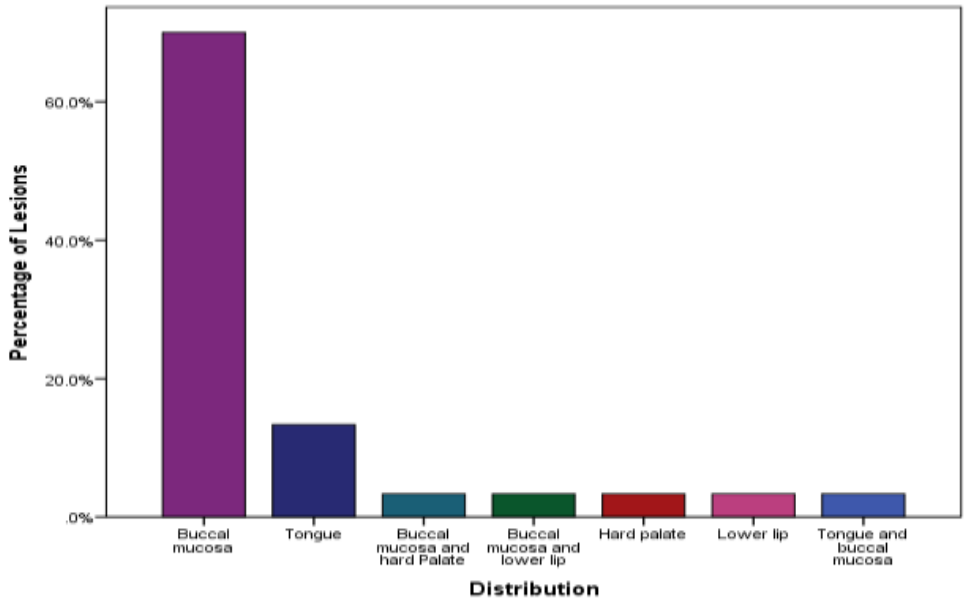

Figure 1 Site of lesions

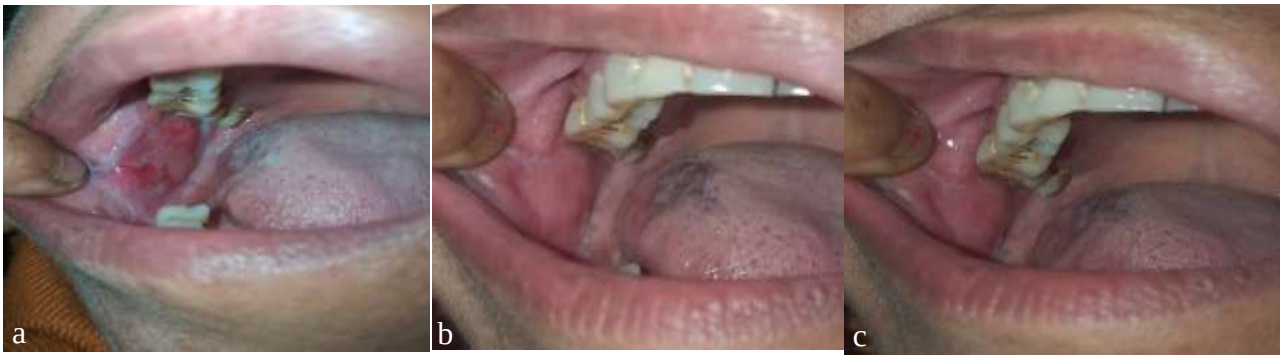

Figure 2 Clinical improvement of lesions over buccal mucosa **a)** Baseline, **b)** 6 Months, **c)** 12 Months

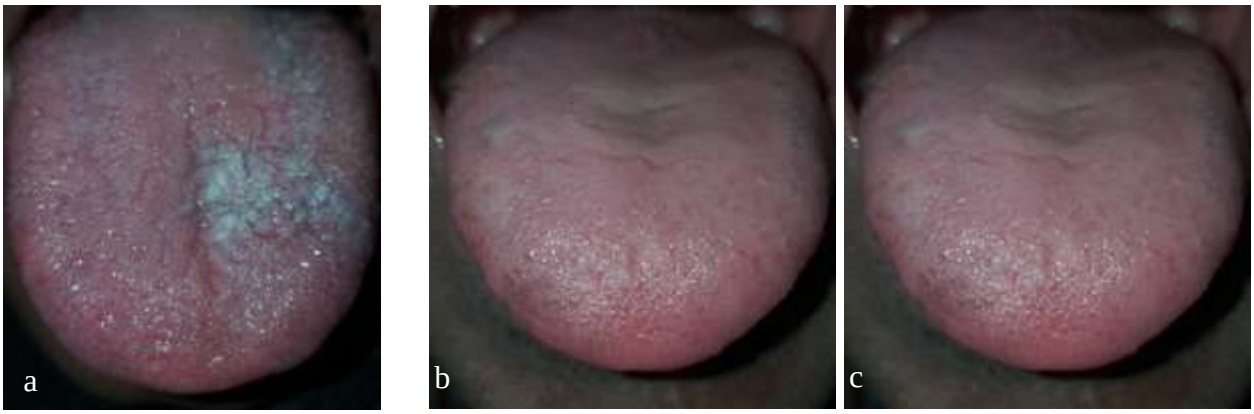

Figure 3 Lesions over tongue. **a)** Baseline, **b)** 6 Months, **c)** 12 Months

In their study, reticular form was predominantly seen in males while erosive and atrophic types were predominantly observed in females. In our study, 80% patients improved significantly during six months of treatment **(Figure 2 & 3)**. 70% lesions were present on buccal mucosa while 13.3% lesions were present on tongue. 3.3% lesions each were present on hard palate

and lower lip. 10% lesions were present on more than one site. 63.3% of the lesions were reticulate and atrophic while 36.7% of the lesions were reticulate and erosive. We also observed a significant decrease in pain with duration of therapy. Our results are in concordance with Rivas-Tolosa *et al.* who studied 8 patients with oral erosive LP (OELP) and these patients were given anti-malarial drugs. In their study, one patient received HCQ 200 mg twice daily for one month and then 200 mg once daily. Remaining 7 patients received chloroquine. All patients had a satisfactory objective clinical response and significant pain relief. These results were evident after a mean time of 2.4 months.[9] The mechanism by which antimalarial drugs are effective in the treatment of OELP is unknown. This also occurs in lupus erythematosus or rheumatoid arthritis, diseases in which the use of these agents is far more common but without a well-characterized pharmacological effect. Their usefulness is probably due to the anti-inflammatory effects of stabilizing lysosomal membranes and inhibition of prostaglandin synthesis and other hydrolytic enzymes.[9] Moreover, it appears that an immune dysfunction mediated by T cells can play a crucial role in the development of oral lichen planus, and increased regulatory T cells in the blood and tissues of patients with oral lichen planus are significantly higher than in healthy controls; antimalarial treatment decreases the expression of these regulatory T cells, which constitute a new therapeutic target in this disease.[6] A more potent effect of antimalarials was recently noted on inhibition of endosomal Toll-like receptor (TLR) signalling resulting in reduced B-cell and dendritic cell activation. This mode of action may also explain the beneficial effects of these drugs in other T-cell-mediated dermatoses such as lupus erythematosus and granulomatous dermatoses like sarcoidosis and granuloma annulare.[10]

Our results are also in concordance with Eisen D who reported that HCQ may be useful in the treatment of OLP.[3] Most of information showing effectiveness of anti-malarial drugs in the treatment of OLP is collected through case reports. De Argila *et al.* described a 51-year-old woman who had had an LP of the lower lip for 11 years. She had undergone several oral and topical therapies with little improvement. The patient had an excellent response to chloroquine phosphate within 3 months.[4] Pallerla *et al.* described a case of severe form of atrophic and ulcerative LP in a 17-year-old female in which they used a combination therapy (antihistamines followed by hydroxychloroquine) for treatment, which resulted in a good prognosis on follow up.[11]

Antimalarials are not free of side effects, and the most common are gastrointestinal symptoms such as nausea, vomiting, and diarrhoea but these are usually mild and are controlled by decreasing the dose of the drug.[12] They also induce mild ophthalmic disorders with the most serious and irreversible adverse effect is retinopathy appears in 1% of cases[11] after 5 years of treatment, and the risk is greater with CQ than with HCQ. The American Academy of Ophthalmology (AAO) screening guidelines recommend that patients be placed on HCQ at ≤6.5 mg/ kg/ day or CQ at ≤3 mg/ kg/ day.[13] In our study, the most common adverse event was gastritis. All of our patients underwent ophthalmic examination at baseline, at completion of therapy, and 6 months after completion of therapy. None of these patients had visual defect. Smoking has also been found to decrease in the efficacy of antimalarial drugs in several studies,[14,15] so it is important to advise patients about the need to give up smoking. In our study, only patient was smoker and the patient were one of the patients who responded poor with the therapy.

The limitations of our study include the small number of patients and lack of control group with another treatment considered first-line to compare results, and evaluation of dose-decreasing effect. However, the remarkable response in our patients contributes clinical evidence about the therapeutic effectiveness of antimalarial agents in the treatment of OLP as previously described by other authors. These data may be useful for the design of future studies to validate our results. In addition, one of the important key designs of our study is longer follow-up up to one year after initiation of treatment which may provide a basis of recommendation of HCQ in the treatment of OLP without any serious adverse effects.

Conclusion

HCQ is a good therapeutic option for OLP due to their easy method of administration, good tolerability, affordable price, and few adverse effects. Although they are not considered first-line drugs for OLP, but our results make it a promising and useful choice for patients who suffer from OLP.

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