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INTERCESSION IN THE MANAGEMENT OF ORAL LICHEN PLANUS: A SYSTEMATIC REVIEW OF THE CURRENT AND NOVEL PHARMACOLOGICAL THERAPIES

[1] Dr. Aniyan K Y, [2]Dr. Ganesan A, [3] Dr. Chandrashekar L K, [4] Dr.Asokan K, [5]Dr. Yesoda Aniyan K

[1] B.D.S, M.D.S in Oral Medicine and Radiology, Senior lecturer, SRM Dental College, SRM University, Concept,research and manuscript writing.
[2] B.D.S, M.D.S, PhD in Oral Medicine and Radiology,Professor, Head of Department, SRM Dental College, SRM University, Manuscript checking.
[3] B.D.S, M.D.S in Oral Medicine and Radiology, Reader, SRM Dental College, SRM University, Review of literature.
[4] B.D.S, M.D.S in Oral Medicine and Radiology, Reader, SRM Dental College, SRM University, Review of literature.

Abstract

Introduction: Oral Lichen Planus (OLP) is a chronic inflammatory, T-cell-mediated autoimmune oral mucosal disease with unconfirmed origin and cause. The medical management of OLP is fraught with challenges.

Aim: The aim was to assess the efficiency of pharmacological interventions used in medical management of OLP.

Materials and Methods: The databases (January 2000 to August 2020):- Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE and EMBASE. All Randomized Controlled Trials (RCTs) for the pharmacological management of OLP which compared active treatment with placebo or between active treatments were considered in this systematic review. Participants of age older than 18 years, gender or race suffering from OLP, and confirmed histopathology have been included. Interventions of all types, including topical medication or systemic drugs of variable dosage, duration & frequency of delivery have been considered. The selected trials were perused by review authors and the data for all the trials were synthesized using specifically designed data extraction form.

Results: A total of 17 RCTs were selected in this systematic review on pharmacological management of OLP. The superiority of any particular management protocol could not be discerned.

Conclusion: The further trials on the management of OLP using pharmacological derivatives demand a larger scale with multiple population sets of various ethnicity, age and gender. Also, the parameters need a more acute standardization for the scrutiny collective.

Keywords: Oral Lichen Planus, Management, Oral lesions, Burning mouth, Mucosal lesions

Summary:

- Oral lichen planus is an intensely disturbing oral condition associated with burning sensation and affects daily living.
- A comparison of different types of pharmacological management protocols in Oral lichen planus.
- Other than the gold standard therapy of steroids, alternative methods of management are discussed along with the dose regimen.

Introduction

The mouth is a reflection of health or disease, often a guard and security alarm. Attributed to the similarity of origin, oral mucosa being derived embryologically from an invagination of the ectoderm, it is also implicated in disorders primarily associated with skin.[1] Oral lichen planus is a chronic inflammatory disease that affects the mucus membrane of the oral cavity. It is propagated as a T-cell mediated autoimmune disease in which cytotoxic CD8+ T cells trigger the apoptosis of basal cells of oral epithelium. Clinically, oral lichen planus (OLP) presents in various forms such as reticular, papular, plaque-like, atrophic, erosive and bullous, of which erosive and atrophic forms are usually symptomatic and need therapeutic interventions. As of now, there is no single definitive cure for this disease entity owing to its recalcitrant nature.[2]A wide spectrum of treatment modalities is available, from topical corticosteroids to laser ablation. These primarily abate the symptoms ranging from burning sensation to mucosal erythema and ulceration. This review deals with the comparison in effectiveness, in randomized controlled trials, various interventions available for the management of this condition varying from the presently used to the most novel modalities.[3]

MATERIALS AND METHODS :

This systematic review was conducted in accordance with the PRISMA guidelines and the objectives were met with the PICOS guidelines.

Eligibility Criteria:

1. Studies with randomized controlled trials and crossover trials which employed different treatment strategies for management of OLP were included.

2. Adult patients above 18 years of age presenting with clinically and histopathological diagnosed OLP

3. Non-randomized, non-comparative, open label and retrospective trials were excluded.

4. Case reports and series were excluded.

5. Studies with patients presenting with OLP as a part of generalized lichen planus were excluded.

6. The search was limited to humans and only studies in English language were included.

Search strategy: Literature exploration was carried out from electronic database of Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE for the timeline , from 1st Jan 2005 to 1st August 2020. The search strategy involved the corresponding search words: MeSH terms in all subheadings: “Oral lichen planus”, “lichen planus”,”pharmacological” “therapy” OR “treatment” OR “therapeutics” OR “management”. Similar search strategy was employed in Cochrane Database. Manual search was performed after perusing the references of the relevant studies. Study selection was done independently in the subsequent stages:

(a) screening of titles and abstracts meeting the inclusion criteria and

(b) screening of the full article identified as relevant.

The RCTs, which compared an active treatment with placebo or active treatment with another active treatment and trials on comparison between 2 different doses or formulation of same treatment, were included.

After thorough scrutiny of the articles, descriptive summary analysis was recorded. The segregated articles were classified for the drug of choice, its mode of delivery, dose, regimen, duration of therapy, length of follow up and records of relapse. The primary outcome was assessment of pain via Visual Analog Scale (VAS) and secondary outcome included clinical resolution of erythema, ulceration, erosion and reticulation. Adverse effects and side effects were also considered as secondary outcome.

RESULTS :

Study selection after the initial search and removing duplication, 321 papers were found. When the titles and abstracts were read and full text screening done, 14 papers were selected for review.(Table 1)

Steroids

High potency steroids are the first line of drug used in the management of OLP. These were recommended as first-line treatment in consensus guidelines published in 2005. [4]They are used as topical and systemic modes of administration. The topical forms are used as mouthwashes, ointments, creams and ora-base. However, due to a better access to posterior areas of mouth and extensile surfaces, mouthwashes are deemed more functional than other forms. However, shortened time of cohesion in topical corticosteroids to the mucosa represents one of their main disadvantages.[5]

Systemic steroids are advised in acute exacerbated and multiple or widespread lesions. Also, in the event of non-response to topical steroids, their use is recommended. It is to be tailored to a dose of 0.5-1mg/kg weight of the patient and must be rapidly tapered once the efficacy is achieved.[6] The preferred regimen is 4 times daily, after meals and before sleep.[5]

The mechanism of action by which the steroids work is two pronged. Steroids, even in topical forms, can significantly reduce the number of HLA DR/T6 in Langerhans cell per mm^2 desquamated epidermal cells. Mucosal and skin cells have the same properties in this regard. Another property of corticosteroids is reducing T lymphocytes activity, which is dependent on Langerhans cells. However, steroids incite localized atrophy, and telangiectasia. It can cause superadded infections like candidiasis. These drugs modulate the gene transcription in the immune system; therefore, this mode of action is not exclusive to the pathogenesis of lichen planus.[5]

Intralesional betamethasone was found to be better for pain relief and resolution of lesion with minimal recurrences and intralesional therapy was found to be more effective than mouthwash due to less adverse

effects (Liu et al, 2013). In a similar vein, intralesional triamcinolone acetonide(TA) was compared to a mouth rinse of TA. The efficacy in terms of VAS, OHIP-14 and objective scoring was comparable in both methods. However, in terms of adverse effects, intralesional methods had a notably positive outcome. Also, the first week assessment, ascertained an improved symptom in intralesional group. (Lee at al,2013). In another study compared, topically applied clobetasol propionate 0.05% to a placebo. The improvement in symptoms was noted in the entire experimental group post 2 months of therapy. Significantly, no adverse effects were recorded(Arduino et al,2018).

From these studies, we concluded that topical steroid is safe, efficacious and cost- effective treatment as first line therapy for OLP. It is important to bear in mind that topical steroid should be used in a form that retains over the lesion for a sufficient amount of time in smallest possible concentration with minimal side effects as the time of contact of medication with the lesion is more important than the concentration of formulation.

Calcineurin inhibitors :

Topical calcineurin inhibitors (TCI) are an established second-line therapy, mainly for atrophic and erosive OLP. Tacrolimus (TAC) application on mucosal lesions for a period of 3 weeks has led to blood level elevation, but within the prescribed norms and without any significant adverse events. It is available in formulations of 0.1% for oral use as ointment, rinse, powder and cream. [6]

The mechanism of action of calcineurin inhibitors is based on the suppression of pro-inflammatory cytokine synthesis. Calcineurin inhibitors inhibit the transcription and production of many pro-inflammatory cytokines by bonding to cytoplasmic proteins of T cell.[7]

In one of the clinical trials, topical pimecrolimus 1% was compared to topical betamethasone 0.1%, 4 times daily, for a period of 4 weeks. It was derived that the topical pimecrolimus application was superior to topical betamethasone in terms of severity of lesion, pain and recurrence rate (Ezatt et al 2019). In another RCT, topical 1% pimecrolimus was applied twice daily for 4 weeks. The follow up parameters of VAS and clinical symptoms improved at the mid-point of the study (Swift et al,2005). The final selected study evaluated a comparison between pimecrolimus 1% and tacrolimus 0.1% cream. It was applied twice daily for 8 weeks, followed by a additional follow-up of two weeks. The net clinical score used for evaluation was found to be decreased in both groups. It was inferred that, both drugs were comparably efficaous with no notable side effects (Vohra et al,2016).

Overall, it was discerned that, calcineurin inhibitors induced a better initial therapeutic response. It does not predispose patients to secondary candidiasis, atrophy or elevated drug levels in blood. However, relapses occurred frequently within 3–9 weeks of the cessation of treatment and the cost of treatment is 5 times higher than the conventional form.[8]

Immunomodulators :

Mycophenolate mofetil (MMF) is a well-tolerated immunosuppressive drug that functions by inhibiting which the proliferation of activated T cells and is reversible in nature. Also, it is touted as an alternative

therapeutic regimen in autoimmune disorders to specifically taper the dose and effects of corticosteroids.[9] It was primarily used to prevent rejection in organ transplant recipients. Also, it has been utilized to treat numerous dermatological conditions, twice a day in dose ranges of 500 and 2000 mg/day.[10] Only a single paper, could be obtained within the norms of the inclusion criteria. The authors stated that the drug concentration (2% MMF), vehicle of delivery as a mucoadhesive patch and duration of 4 weeks were all key factors in the significant finding obtained (Samiee et al.2020).

Hyaluronic acid (HA)is a linear polymer of glucuronic acid, N-acetylglucosamine disaccharide. It is an immunostimulant and functions by tissue healing wherein it stimulates angiogenesis, reduces exudation, is vaso-protective, and induces fibro genic action.[11] According to Nolan et al. there is evidence of its inherent analgesic action due to its barrier effect. [12]An additional favorable property, it is an ideal biomaterial for cosmetic, medical, and pharmaceutical applications owing to its biocompatibility, non-immunogenicity, biodegradability, and viscoelasticity. Current research by Hashem et al. only reports the topical use HA in OLP.[11]

Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG-PSN), the third-generation BCG extract containing immunologic active materials, polysaccharide and nucleic acid, can regulate the subsets of T cells (CD4 and CD8 cells) and subtypes of helper T cells by the principle of immunosuppression. The process of extraction and removal of proteins removes the adverse effects of swelling and fever associated with the vaccine. [13]It was initially uses as a preventive measure in tuberculosis and malignancy. The short-term efficacy of topical BCG-PSN was comparable to the standard topical TA in regard to relapse and recurrence (Xiong et al, 2009).

Thalidomide is an anti-inflammatory and anti-immunologic drug with T-cell function. The mechanism of action is in essence by immunosuppression by its ability to decrease production of TNF-alpha. In addition, systemic thalidomide is a recognized alternative medication for refractory cases of erosive OLP that are insensitive to systemic glucocorticoids.[17] The only available and researched form of this medication is the topical form. Also, the authors did not report any adverse effects and relapse. The efficacy of the drug was determined to be comparable to corticosteroid use (Wu et al,2010).

Nutraceuticals :

Curcumin is a natural phytochemical and the active component of turmeric. Curcumin and its oily extracts have demonstrated antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities in multiple disease processes.

Aloe vera :

Aloe vera (AV) is widely used as a natural treatment and alternative therapy for a variety of diseases, and have proved to be healing, cosmetic, and nutritional.[19] AV acts by inhibiting the inflammatory process by its interfering action on the arachidonic acid pathway via cyclooxygenase and by the reduction of leucocyte adhesion and TNF-a level. [20] In a study of AV gel in the treatment of OLP, positive effects was demonstrated. The authors published that 81% of the patients demonstrated improvement (Choonhakarn et al,2008). Another study demonstrated similar findings in improved pain, the oral lesions, and the oral

quality of life. Also, no adverse effects were observed in the course of the study (Salazar-Sanchez et al,2010).

Conclusion: A comparative statistical analysis was not possible owing to the multitude of variations in the drug concentration, vehicle for delivery, regimen and controls used. However, it was discernable that steroids still persist as the principle mode of therapy and that on use of nutraceuticals, an adverse effect free disease free period could be achieved. The further trials on the management of OLP using pharmacological derivatives demand a larger scale with multiple population sets of various ethnicity, age and gender. Also, the parameters need a more acute standardization for the collective scrutiny

Conflicts of Interest: There are no conflicts of interest and this study was unsupported financially by any sponsors or intellectual bodies.

References :

1. Gupta Sonia, Jawanda K Manveen. Oral Lichen Planus: An Update on Etiology, Pathogenesis, Clinical Presentation, Diagnosis and Management. Indian J Dermatol. 2015 May-Jun; 60(3): 222–229.
2. Saawarn N, Shashikanth M C, Saawarn S, Jiege V, Chaitanya NC, Pinakapani R. Lycopene in the management of oral lichen planus: Aplacebo-controlled study. Indian J Dent Res.2011:22:639-43
3. N.Lavanya, P Jayanthi, Umadevi K Rao,K Ranganathan.Oral Lichen Planus: An update on pathogenesis and treatment.J Oral Maxillofac Pathol.2011 May-Aug;15(2):127-132.
4. Ahadian H.a , Akhavan Karbassi MH.a , Vahidi AR.b , Owlia F. Comparison of Two Corticosteroids Mouthwashes in Treatment of Symptomatic Oral Lichen Planus. J Dent Shiraz Univ Med Scien. 2012 June; 13(2): 49-53
5. Ezzat Ola M, Helmy Iman M.Topical pimecrolimus versus betamethasone for oral lichen planus: a randomized clinical trial. Clin Oral Invest.2018 June
6. Mirza S, Rehman N, Alrahlah A, Alamri WR, Vohra F. Efficacy of photodynamic therapy or low level laser therapy against steroid therapy in the treatment of erosive-atrophic oral lichen planus. Photodiagnosis Photodyn Ther. 2018 Mar;21:404-408. doi: 10.1016/j.pdpdt.2018.02.001.
7. H. Husein-elahmed, U Gieler, Martin Steinhoff. Lichen planus: a comprehensive evidence-based analysis of medical treatment.journal of european academy of dermatology and venerology.2019 october;33(10):1847-1862.
8. Siponen M, Huuskonen L, Kallio-Pulkkinen S, Nieminen P, Salo T. Topical tacrolimus, triamcinolone acetonide, and placebo in oral lichen planus: a pilot randomized controlled trial. Oral Dis. 2017 Jul;23(5):660-668.
9. Gutfreund K, Bienias W, Szewczyk A, Kaszuba A. Topical calcineurin inhibitors in dermatology. Part I: Properties, method and effectiveness of drug use. Postepy Dermatol Alergol. 2013 Jun;30(3):165-9. doi: 10.5114/pdia.2013.35619. Epub 2013 Jun 20.
10. Jajarm, Hasan Hoseinpour; Falaki, Farnaz; Sanatkhani, Majid; Ahmadzadeh, Meysam; Ahrari, Farzaneh; Shafaee, Hooman. A comparative study of toluidine blue-mediated photodynamic

therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial. Lasers in Medical Science, 30(5), 1475–1480.

11. Hashem AS, Issrani R, Elsayed TEE, Prabhu N. Topical hyaluronic acid in the management of oral lichen planus: A comparative study. J Invest Clin Dent. 2019;10:e12385.
12. Nolan A, Baillie C, Badminton J, Rudralingham M, Seymour RA. The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. J Oral Pathol Med. 2006;35:461-465.
13. Zhou G, Fan MW, Liu JY. Regulation of BCG-polysaccharide nucleic acid on Thl／Th2 cytokines from peripheral blood mononuclear cells in oral lichen planus. Chin J Dent Res 2004; 7: 5–10
14. C. Xiong, Q. Li , M. Lin, X. Li , W. Meng , Y. Wu, X. Zeng , H. Zhou, G. Zhou. The efficacy of topical intralesional BCG-PSN injection in the treatment of erosive oral lichen planus: a randomized controlled trial. J Oral Pathol Med (2009) 38: 551–558.
15. Michael EF, Gordon RM, William DF. Thalidomide. Lancet 2004;363:1802-11

16. Salazar-Sanchez et al. Efficacy of topical Aloe vera in patients with oral lichen planus: a randomized double-blind study. J Oral Pathol Med (2010) 39: 735–740.

21.Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. The efficacy of aloe vera gel in the treatment of oral lichen planus: a randomized controlled trial. Br J Dermatol 2008; 158: 573–7.

22. Mansourian et al. Comparison of Aloe Vera Mouthwash With Triamcinolone Acetonide 0.1% on Oral Lichen Planus: A Randomized Double-Blinded Clinical Trial. Am J Med Sci 2011;342(6):447–451.

Table 1: Selected papers and categorization Medical intervention	Author and year	Sample	Outcome	Time	Follow	Relapse	Adverse effects
Steroids	Liu et al 2013	n=29-1.4mg Intralesional betamethasone n=30-8mg intralesional triamcinolone acetonide R=Once a week for 2 weeks	1.Visual Analogue Scale (VAS) 2.Physician Global Assessment, 3.Ordinal & Nominal scales of self-assessment. 4.Oral Mucositis Assessment Scale.	2	12	E=45% C=14	Nil
	Lee et al. 2013	n=20- TA 0.4% mouth rinse R=Thrice daily n=20- intralesional injection of 0.5 mL TA (0.40mg/ml)	1.VAS 2.OHIP-14	6 weeks	52	E=20% C=40%	E=44% C=5%
	Arduino et al,2018	n=16-0.05%clobetasol propionate n=16-4% hydroxyethyl cellulose R=Twice daily	1. VAS 2. Thongprasom et al criteria scale	8	24	E=37% P=50%	

Calcineurin inhibitors	Vohra et al,2016	n=15- 1 % Pimecrolimus cream n=15-0.1% Tacrolimus Ointment R=Twice daily	VAS Thongprasom et al criteria scale	8	12	Nil	E=6% C=40%
	Passeronet al.2007	n=6-1% Pimecrolimus cream n=6-Placebo cream R=twice a day	VAS	4			
	Swift et al.2005	n=10-1%Pimecrolimus cream n=10-Placebo cream	VAS Lesion size	4	Biweekly		Nil
	Ezzat et al.2018	n=15-1% Pimecrolimus cream n=15-0.1% Betamethasone valproate cream R=4 times a day		4 weeks	4		C
Mycophenolate mofetil	Samiee et al, 2020	n=15-2% Mycophenolate mofetil in mucoadhesive patch n=8-Placebo R=twice a day	VAS Lesion size	4 weeks			
Hyaluronic acid topical ointment	Hashem et al,2018	n=0.1% Triamcinolone acetonide n= 0.2% Hyaluronic acid R=Thrice a day	VAS Lesion size and erythema	4 weks			
	Nolan et al,2009	n=62-0.2% Hyaluronic acid n=62-Placebo	1.Thongprasom scale 2.VAS	4 weeks			

BCG PSN	Xiong et al,2009	n= 31-intralesional injection with 0.5 ml BCG-PSN R=6 times over 2 weeks n=25-intralesional injection of 10 mg TA (40 mg／ml) R=Once a week	1.VAS 2. Lesion size	2 weeks			
Thalidomide	Wu Yun et al,2010	n=33- 1%thalidomide paste n=30-0.4% TA paste		4 weeks			
Curcumin	Kia et al, 2020	n=80mg nano curcumin soft gel capsule R=once daily		12 weeks			
	Nosratzehi et al, 2017	n=20-Mucoadhesive paste R=Thrice daily n=0.1% Betamethasone solution R=Thrice daily		12 weeks			
Aloe vera	Choonhakarn et al.2008	n=27-70% concentration (AV)(0.4 ml) n=27-Placebo R=Thrice daily		8 weeks			
	Salazar-Sa´nchez et al.2010						
	Mansourian et al.2011	n=70% concentration (0.4 ml) three times a day for 12 weeks					

BCG-PSN -Bacillus Calmette-Guerin polysaccharide nucleic acid

TA-Triamcinolone acetonide

AV-Aloe ver