Review Article

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Effectiveness of hyaluronic acid in the management of oral lichen planus: a systematic review and meta-analysis

Manjushri Waingade[1], Raghavendra S Medikeri[2], Shamali Gaikwad[1]

[1]Department of Oral Medicine and Radiology, Sinhgad Dental College and Hospital, Pune, Maharashtra, India
[2]Department of Periodontology, Sinhgad Dental College and Hospital, Pune, Maharashtra, India

Oral lichen planus (OLP) is a chronic inflammatory immune-mediated condition that has been identified as a potentially malignant oral disorder. Various therapies have been proposed for its management as alternative to corticosteroids. However, no definitive treatment has been identified that can result in complete remission or minimal recurrence. Hyaluronic acid has recently been used as an alternative therapy for the management of OLP. This study aimed to systematically review the effectiveness of Hyaluronic acid in the management of symptomatic OLP. Online electronic databases and manual searches were performed for randomized controlled trials (RCTs) published in English between January 2010 and April 2022. RCTs were identified that compared the efficacy of hyaluronic acid and other interventional therapies at baseline and during follow-up. The Cochrane Risk of Bias tool was used to assess the quality of the included studies. Visual analog scale (VAS) scores, Thongprasom sign scores, lesion size, degree of erythema, clinical severity, and disease severity were assessed both quantitatively and qualitatively. Seven studies were analyzed. Five studies reported a high risk of bias while the remaining two studies reported an unclear risk of bias. The overall quantitative assessment of size, symptoms, degree of erythema, and sign score in OLP lesions treated with HA was not statistically significant compared to that in the control group ($P > 0.05$). In addition, subgroup analysis comparing HA with placebo or corticosteroids did not yield statistically significant ($P > 0.05$) results. Qualitatively, both HA and tacrolimus resulted in an effective reduction in signs and symptoms. Clinical/disease severity index/scores were inconsistent. A high degree of heterogeneity was observed among the included studies. None of the included studies reported the side effects of HA. These findings suggest that corticosteroids, tacrolimus, placebo, and HA could be equally effective in OLP management. The clinical/disease severity index or score reduction cannot be determined with certainty. Thus, OLP can be treated with HA as an alternative therapy. Owing to limited clinical trials on HA, high heterogeneity, and high risk of bias in the included studies, definitive conclusions cannot be derived.

Keywords: Corticosteroids; Hyaluronic Acid; Oral Lichen Planus.

INTRODUCTION

Oral lichen planus (OLP) is a chronic immune condition characterized by remission and flares. It is more common in females aged > 40 years and in non-Asian countries [1,2]. OLP has a worldwide prevalence of 1.01% and overall global prevalence of 0.89%. The pathogenesis is postulated to be a chronic disease of the oral mucosa mediated by an antigen-specific mechanism that activates T-cells concomitant to a non-specific mechanism of mast cell degranulation [1-4].

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Corresponding Author: Manjushri Waingade, Professor, Department of Oral Medicine and Radiology, Sinhgad Dental College and Hospital, Sinhgad road, S.No 44/1, Vadgaon (Bk), Pune, Maharashtra, India
Phone: +91 7875044983 E-mail: manju.waingade@gmail.com

Corticosteroids remain the “gold standard" for the treatment of OLP [1,4]. The primary objective of treatment is the elimination of painful symptoms and healing of ulcerative lesions. Since OLP is a chronic disease, decreasing the frequency of relapses and prolonging symptom-free periods is the most important requirement for patients and clinicians [3,5-7]. However, to date, no treatment for OLP has been completely curative because of its recalcitrant nature and idiopathic etiology, and most available treatment modalities have focused on eliminating the signs and symptoms of the disease [3,8]. Current therapies have local and systemic adverse effects, and lesion recurrence occurs after treatment is discontinued [3,4,7,9].

Hyaluronic acid (HA) offers advantages over topical steroids in that it is safe to use in all patients, including infants and pregnant women, who may be reluctant to use steroids. It can be used in all grades of oral ulceration [10-12]. HA plays an important role in various biological processes, such as cell signalling, morphogenesis, matrix organization, tissue hydration, lubrication, wound healing, regulating gene expression, and cell proliferation [8,13-15]. HA is commercially available as sodium hyaluronate combined with polyvinylpyrrolidone (PVP) and glycyrrhetinic acid. Sodium hyaluronate coats the oral mucosa, thereby enhancing tissue hydration and accelerating healing. PVP is a hydrophilic polymer with mucoadherent and film-forming properties that enhance tissue hydration. Glycyrrhetinic acid is a breakdown product of glycyrrhizin, the active component of licorice, which has anti-inflammatory properties and aids ulcer healing [11,13,16].

Topical HA helps reduce discomfort and accelerates healing of patients during the postoperative period and in both implant and sinus lift procedures during the postoperative period. It can be used as an adjunct in the treatment of gingival diseases and chronic periodontitis, and local HA can be a valuable treatment for oral ulcers [12,16,17].

However, despite HA showing promising properties, data for its usage in OLP remain scarce and conflicting [6,15,18-20]. Previous systematic reviews have compared the efficacy of topical HA with only steroids/placebo [21]. Thus, the aim of this systematic review was to carefully analyze the effectiveness of HA in the management of OLP in comparison with placebo or any other intervention.

METHODS

Protocol development: This systematic review was written and completed based on the PROSPERO Declaration on Preferred Reporting Products for Systematic Reviews and Meta-Analyses (registration number: CRD42021228529). The research question focused on addressing the effectiveness of HA in the management of OLP compared to that of local or topical corticosteroids/placebo therapy/any other intervention.”

Eligibility criteria

Randomized controlled trials (RCT) on OLP patients diagnosed clinically and/or histologically published in English language from the period of January 2010 to April 2022 were included in the study. Case reviews, case series, in vitro studies, letters to the editor, abstracts, animal experiments, non-randomized controlled studies, and unpublished data were excluded.

Participants/population: Adult patients (aged ≥ 18 years) clinically and/or histologically diagnosed with OLP.

Intervention(s) / exposure(s): Hospital in/out-patients diagnosed with OLP lesions treated by application of topical ointments, intralesional injections, mouth washes, or rinsing with HA alone.

Comparator(s)/control: Hospital in/out-patients diagnosed with OLP lesions should be treated by application of topical ointments, intralesional injections, mouth washes, rinsing corticosteroids, placebo, or any other intervention.

Main outcome(s): Changes in pain scores (VAS), Thongprasom sign scores, degree of erythema, clinical or disease severity index/scores, and size of lesions from

baseline to the last available follow-up.

Search strategy: From January 1, 2010, to April 1, 2022, researchers (MW, RM) scanned databases such as PubMed/MEDLINE, PMC, Cochrane library, clinical trial registry, Google Scholar, Science Direct, Directory of Open Access Journals (DOAJ), and manual references of included studies. The search terms were adapted for use with other bibliographic databases in combination with database-specific filters for controlled trials, where these were available. The following mesh terms and keywords were used in the electronic database search.

1. PMC: (((((((("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields]) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "hyaluronan"[All Fields])) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR ("sodium"[All Fields] AND "hyaluronate"[All Fields]) OR "sodium hyaluronate"[All Fields])) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR ("amo"[All Fields] AND "vitrax"[All Fields]) OR "amo vitrax"[All Fields])) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "biolon"[All Fields])) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "etamucine"[All Fields])) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "healon"[All Fields])) OR ("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields] OR "amvisc"[All Fields])) AND ("lichen planus, oral"[MeSH Terms] OR ("lichen"[All Fields] AND "planus"[All Fields] AND "oral"[All Fields]) OR "oral lichen planus"[All Fields] OR ("oral"[All Fields] AND "lichen"[All Fields] AND "planus"[All Fields]))
2. PubMed: (((((((hyaluronic acid) OR (Hyaluronan)) OR (Sodium Hyaluronate)) OR (Amo Vitrax)) OR (Biolon)) OR (Etamucine)) OR (Healon)) OR (Amvisc)) AND (Oral lichen planus)
3. Cochrane library - hyaluronic acid in Title Abstract Keyword OR Hyaluronan in Title Abstract Keyword OR Healon in Title Abstract Keyword OR Biolon in Title Abstract Keyword AND oral lichen planus in Title Abstract Keyword - in Trials with 'Pain, Palliative and Supportive Care', 'Wounds', 'Oral Health', 'Child Health' in Cochrane Groups (Word variations have been searched)
4. Clinicaltrials.gov: Oral Lichen Planus and Hyaluronic Acid
5. DOAJ: Oral Lichen Planus and Hyaluronic Acid
6. Science Direct: Oral Lichen Planus and Hyaluronic Acid
7. Google Scholar: allintitle: Hyaluronic Acid AND Oral Lichen Planus

Screening process: Two independent reviewers conducted the searching and screening (MW and SG). Following the removal of duplicates, all recovered articles were initially screened for titles and abstracts, and unrelated studies were eliminated. For possible data retrieval, the full text of the qualifying studies were collected and carefully reviewed according to eligibility requirements (inclusion/exclusion). The authors of the included studies were contacted via email to confirm any concerns or missing details.

Data extraction and synthesis: Relevant data from the included publications were collected from the data extraction files. The reviewers first determined the eligibility of each study for inclusion in the systematic review based on the reported parameters. The following information was collected: study population, type of OLP, description of therapy, outcome measurements, results, adverse effects, and conclusions. Both qualitative and quantitative syntheses were considered when the data were combined. A meta-analysis was performed to

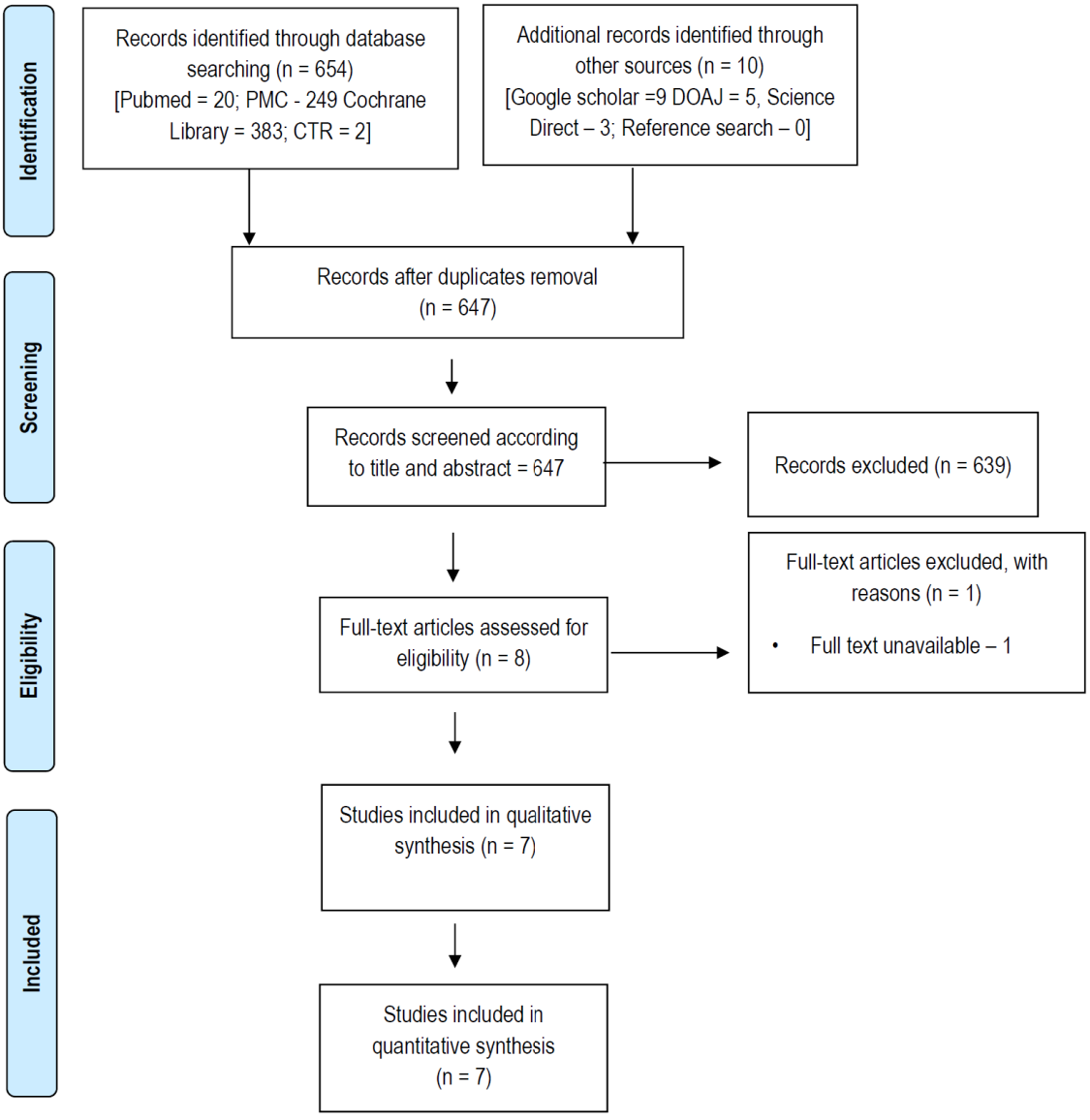

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (2020) flow diagram of the search strategy. CTR, Clinical trial Registry; PMC: PubMed central; DOAJ, Directory of open access Journal; n, number; RCT, randomized controlled trials.

evaluate the significant differences in the outcomes of HA and other interventions. The mean differences in the VAS scores, Thongprasom sign scores, and lesion size following both therapies were calculated. A fixed-effects model was used wherein the heterogeneity was shown to be low ($I^2 \leq 50\%$), and a random-effects model was used wherein the heterogeneity was high ($I^2 > 50\%$). All analyses were performed using the RevMan Manager 5.3 software (Cochrane, London, UK).

Quality assessment: The overall quality of each included study was evaluated using the Cochrane Risk of Bias tool (ROB-2 tool) (http://ohg.cochrane.org) for RCTs [22]. The overall risk of bias was determined as low / with some concerns / high. Disagreements between the review authors over the risk of bias in particular studies were resolved by discussion with the involvement of a third reviewer, whenever necessary.

RESULTS

A systematic search of the electronic databases yielded

Table 1. Characteristics of included studies

Sr. No	Study	OLP type	Patients	Case description	Outcome measurements	Outcomes		Adverse effects	Conclusion
						Pain (VAS)			
1	Youssef et al., 2019 [13]	Erosive OLP	20 patients	Group I (10): topical corticosteroids in orabase 4-5 times daily for 28 days Group II (10): HA gel 4-5 times daily for 28 days	Thongprasom sign score: baseline, 1 month & 3 months. Pain (VAS): graded overall severity of their symptoms at baseline, 10 days and 3 months.	Pain differences (VAS):		Nil	Topical application of HA 0.2% appears to be significantly more effective in the control of the symptoms of OLP when compared to topically applied corticosteroid.
						Group I: 1.60 ± 0.52	Group II: 6.80 ± 1.55		
						Thongprasom sign score			
						After 1 month:			
						Group I : 2.40 ± 0.52	Group II: 3.20 ± 0.79		
						After 3 months:			
						Group I : 1.0 ± 0.67	Group II: 1.80 ± 0.42		
2	Bruckmann et al., 2020 [15]		9 patients (8 F, 1 M, mean age 48 (18–71) yrs)	Case (7): Hyaluronic acid gel 0.2% 4 g of fluid 3 times/day for 2 min Control (2): Placebo (methylcellulose 400) 4 g of fluid 3 times/day for 2 min	1. Total amount of saliva 2. pH of saliva, 3. CSI 4. OHIP-G 5. VAS for pain intensity. 6. Salivary Cytokines levels (IL-6) & Calprotectin levels 7. Periodontal microbiota All parameters were assessed at the beginning, after 6 weeks, and 12 weeks	Amount of saliva: Baseline - 1.0 ± 0.8 g		Nil	Salivary parameters did not differ significantly No Significant changes noted in CSI, pain scores, periodontal microbiota & gingival index (GI). mean plaque index (PI) showed significant changes between HA and placebo.
						Control	HA		
						Increased by 0.3 ± 0.5 g	Increased by 0.3 ± 0.5 g		
						Saliva pH: baseline - 6.7 ± 0.4			
						Control: decreased by −0.4 ± 0.8	HA: decreased by −0.4 ± 0.4		
						IL-6 levels: baseline – 1.6 ± 1.6 pg/mL			
						Control: 0.4 ± 0.4 pg/mL	HA: 0.2 ± 0.4 pg/mL		
						Calprotectin: Baseline - 12.9 ± 13.2 pg/mL			
						Control : 4.0 ± 9.7 pg/mL	HA: 3.0 ± 18.1 pg/mL		
						Periodontal Microbiota Baseline: Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola, Fusobacterium nucleatum	Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Fusobacterium nucleatum, Capnocytophaga species Control: Fusobacterium nucleatum		
						Periodontal Parameters: Baseline GI: 0.8 ± 0.3			
						Control: −0.1 ± 0.4	HA: 0.0 ± 0.3		
						Baseline PI: 0.4 ± 0.3 v/s Control: 0.0 ± 0.3 (control) & 0.1 ±0.3 (HA)			
						Clinical Severity Index: Baseline (2 ± 1) v/s Control (0.0 ± 0.5) & HA (−0.3 ± 0.5)			
						Pain : Baseline (2.6 ± 1.6) v/s Control (-1.5 ± 2.9) & HA (-1.4 ± 2.2)			

664 studies. After removing duplicate records (n = 17) using Mendeley software and screening titles and abstracts, eight full-text studies were evaluated. Seven studies were included in the final review of the qualitative and quantitative assessments. The PRISMA flowchart for the inclusion of studies is shown in Figure 1. The findings of this meta-analysis were based on seven RCTs comprising 154 patients.

Table 1. Characteristics of included studies (continued)

Sr. No	Study	OLP type	Patients	Case description	Outcome measurements	Outcomes	Adverse effects	Conclusion
						Pain (VAS)		
3	Hashem et al., 2018 [18]	Erosive (N = 11) Atrophic (N = 8) and Combined (N = 1)	40 patients	Group I (20): topical TA preparation (0.1%) 3 times /day Group II (20) : topical HA preparation (0.2%) 3 times /day	Severity of pain using the VAS Degree of erythema assessed by modified oral mucositis index. The degree of erythema & graded as mild, moderate, and severe. Size of an ulcer or erosive area was measured in millimeters. Evaluation was done at the beginning of the study [baseline], and then it was reassessed after 14, 21, and 28 days	VAS scores (group 1 v/s group 2): Baseline: 4.04 ± 1.05 v/s 7.82 ± 1.02 Day 28: 1.3 ± 0.85 v/s 1.42 ± 0.87 Degree of erythema: Baseline: 2.18 ± 0.74 v/s 1.82 ± 0.88 Day 28: 0.50 ± 0.41 v/s 0.62 ± 0.53 Size of erosive area: Baseline: 9.5 ± 5.95 v/s 8.96 ± 5.67 Day 28: 2.39 ± 1.8 v/s 2.56 ± 1.67	Nil	Topical 0.2% HA is effective in reducing pain and the clinical signs of OLP. Statistically, no significant difference was seen between the groups when the degree of erythema was compared at any of the time intervals.
4	Shetty RR et al. 2016 [6]	Reticular-39 Erosive-6 Atrophic-3 Desquamative gingivitis-1 Pigmented-1	50 patients Case group: 13 M and 11 F patients with age range of 19-75 yrs. Control group:11 M and 14 F patients with age range of 26-70 yrs	Case (25): received topical 0.2% hyaluronic acid gel for 14 days. Control (25): topical placebo.	Severity of pain using the VAS. Intensity of erythema was measured using the modified oral mucositis index. Size of an ulcer or erosive area was measured in millimeters. Evaluation was done at the beginning of the study [baseline], and then it was reassessed after 7,14, 21, and 28 days.	VAS scores Baseline: Case (7.08 ± 1.53) Control (7.96 ± 1.14) Day 28: Case (1.48 ± 1.42) Control (7.76 ± 1.39) Degree of erythema: Baseline: Case (1.96 ± 0.35) v/s Control (1.64 ± 0.64) Day 28: Case (0.48 ± 0.59) v/s Control (1.36 ± 0.70) Size of erosive area: Baseline: Case (8.28 ± 6.76) v/s Control (8.67 ± 5.32). Day 28: Case (2.59 ± 1.76) v/s Control (9.05 ± 5.08)	Nil	Topical hyaluronic acid 0.2% reduced the subjective symptoms of burning sensation degree of erythema and the mean area of the lesions than compared to the control group on placebo
5	Nolan A et al., 2009 [14]	Atrophic-ulcerative	124 adults Case group : 9 M and 53 F average age 55.3 yrs Control group : 15 M and 47 F average age 56.46 yrs	Case (62): Patients received topical 0.2% hyaluronic acid gel for 4–5 times a day application for the next 28 days. Case (62): Patients received topical placebo gel for 4–5 times a day application for the next 28 days.	1. Severity of pain using the 100-mm VAS Recordings were made at 5 min, 60 min, 2, 3 and 4 h post-applications. 2. The size of any ulcer or erosive area was measured with calipers. 3. Thongprasom sign score Evaluation was done at the beginning of the study [baseline], and then it was reassessed after 15 and 29 days.	VAS Score: Baseline: Case (40) v/s Control (40) After 4 hrs : Case (28) v/s Control (30) Size of erosive lesion : Baseline: Case (16.1 ± 0.7) v/s Control (15.5 ± 0.7) Day 29 : Case (13 ± 0.7) v/s Control (13.5 ± 0.72) Thongprasom's Criteria: Placebo and 0.2% HA had no effect on the extent and severity of the OLP.	Nil	No significant results were seen in case of pain and signs While significant results seen in case of size of erythema Topical HA (0.2%) does have some benefits in the management of OLP.

Five studies reported a high risk of bias [6,14,15,18,19] due to one or more risks owing to performance, detection, attrition, and reporting bias. Two other studies reported an unclear risk of bias in selection, performance, and detection [13,20].

Table 1 provides comprehensive information pertaining to the included studies.

Quantitative assessment of the size of the OLP lesion was performed using pooled overall data. A total of 214 participants from three studies were included to analyze the size of OLP lesions [6,14,18]. Two studies compared HA with placebo treatment, while another study

Table 1. Characteristics of included studies (continued)

Sr. No	Study	OLP type	Patients	Case description	Outcome measurements	Outcomes	Adverse effects	Conclusion
						Pain (VAS)		
6	Santonocito et al., 2021 [20]		38 patients Case group 20 patients (10 M and 10 F) mean age of 62.5 ± 9.13 Control group 18 patients (8 M and 10 F) mean age of 65.55 ± 9.61	Case (20): Anti inflammatory mouthwash (calcium hydroxide, hyaluronic acid, umbelliferone and oligomeric pro-anthocyanidins) used pure and without dilution at a dosage of 20 mL, 3 times a day Control (20): 0.05% clobetasol propionate gel 2 times a day	1. Clinical grading of the lesions by Thongprasom et al. 2. Pain and burning by Numerical Pain Scale. After baseline, patients were followed for three months of therapy	Clinical grading (Thongprasom et al) Baseline: Clobetasol (3) v/s HA (1). 3 months: Clobetasol (2.5) v/s HA (1.5) Symptoms Score (Numerical Pain Score (NRS) Score) Baseline: Clobetasol (4.67 ± 2.25) v/s HA (3.05 ± 1.23) 3 months: Clobetasol (2.33 ± 1.64) v/s HA (1.85 ± 1.23)	Nil	Clobetasol seems to be treatment of first choice in the most severe forms of OLP as the study showed that the anti-inflammatory has a limited ability to induce remission of signs in subjects with severe forms of OLP, compared with clobetasol
7.	Polizzi et al.,2021 [19]	Atrophic or ulcer-erosive and reticular or plaque type of OLP	38 patients 21 F and 17 M, with a mean age of 65 ± 12.5 yrs	Case (19): mouthwash containing calcium hydroxide 10%, hyaluronic acid 0.3%, umbelliferone, and oligomeric proanthocyanidins rinse the oral cavity with 10–20 ml Control (19): topical Tacrolimus ointment 0.1% applied twice daily After baseline follow up was done once month for three months.	Symptom scale according to Raj et al. Signs scale developed by Kaliakatsou et al. combining both OLP symptoms and sign scores, the Disease severity score was recorded, according to Singh et al.	OLP Symptom Baseline: Case (2.21 ± 1.40) v/s Control (2.05 ± 0.71) 3rd Month: Case (0.61±0.37) v/s Control (0.84±0.31) OLP Sign Baseline: Case (3.06 ± 1.95) v/s Control (1.84 ± 1.99) 3rd Months: Case (1.11±0.46) v/s Control (1.53 ± 0.70) OLP Disease Severity Baseline: Case (5.47 ± 2.44) v/s Control (3.89 ± 2.70) 3rd months: Case (1.85 ± 0.77) v/s Control (2.37 ± 0.74)	Nil	Both treatments were effective in the reduction of OLP signs and symptoms.

CSI, Clinical Severity Index; F, female; GI, gingival index; h, hours; HA, hyaluronic acid; IL, interleukin; M, male; min, minute; N, number; OHIP-G, oral health impact profile questionnaire German version; OLP, oral lichen planus; PI, plaque index; TA, triamcinolone; VAS, visual analogue scale; yrs, years.

compared HA with corticosteroid treatment. The overall pooled mean difference was -1.97 [-4.30 0.36], which was not statistically significant in favor of the HA drug (Z = 1.66, P = 0.10) compared to that of cortico-steroids/placebo. There was high heterogeneity (I^2 = 94%, P < 0.00001) reported among the studies (Fig. 2A). In addition, subgroup analyses were performed to determine the effects of HA and the placebo (Fig. 2B). Two studies showed a statistically non-significant effect (Z = 1.14; P = 0.26). One study compared HA to corticosteroid, and their results illustrated that 0.2% HA was effective in reducing pain at the end of 28 days in the treatment of OLP [18].

A total of 199 participants from 6 studies were included in the analysis of OLP lesion symptoms [6,13,15,18-20]. The pooled overall mean difference was 0.65 [95% CI: -1.80 to 3.09] which was not statistically significant (Z = 0.52, P = 0.60). There was high heterogeneity (I^2 = 99%, P < 0.00001) reported among studies (Fig. 3A). Three studies compared HA with corticosteroids and two studies compared HA with a placebo [6,13,15,18,20]. Quantitative subgroup analysis comparing HA to placebo and corticosteroids yielded statistically non-significant results (Z = 0.09, P = 0.92 and Z = 1.03; P = 0.30, respectively) (Fig. 3B,C). One study examined the use of the drug tacrolimus in treating OLP symptoms and concluded that both 0.3% HA and topical 0.1% tacrolimus ointment twice daily were similarly effective in resolving OLP symptoms at 3 months [19].

Only two studies (90 participants) compared the degree of erythema [6,18]. The pooled mean difference was -0.37 [95% CI: -1.35 − 0.61], which was not statistically significant (Z = 0.75, P = 0.45). High heterogeneity (I^2 = 94%, P < 0.0001) was observed among the studies (Fig. 4).

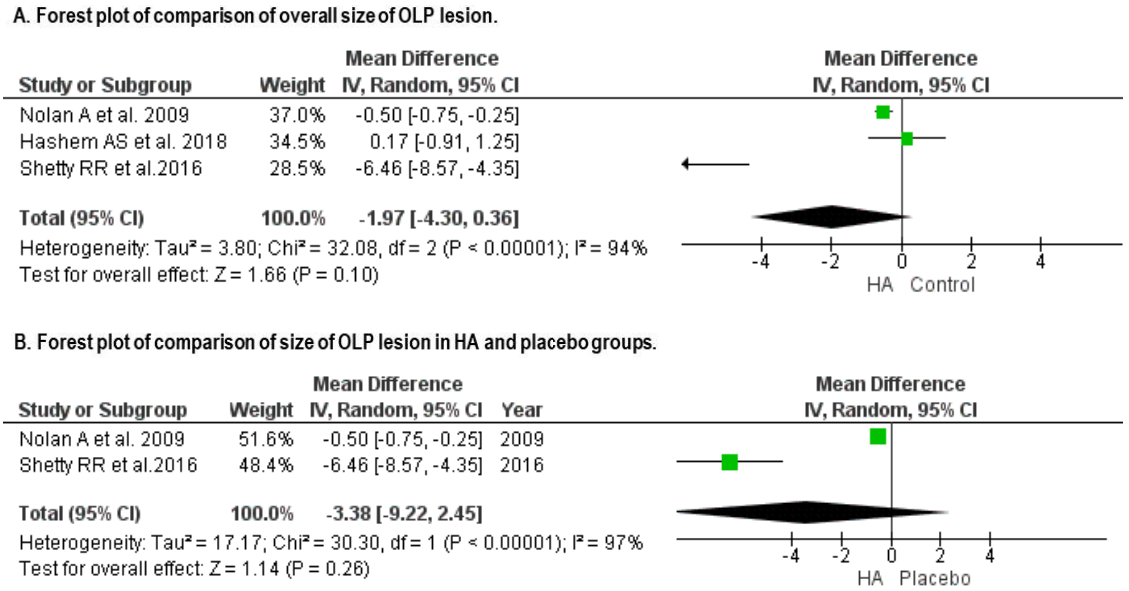

Fig. 2. Forest plot of comparison of size of the OLP lesion. CI, confidence interval; HA, hyaluronic acid; IV, inverse variance; OLP, oral lichen planus.

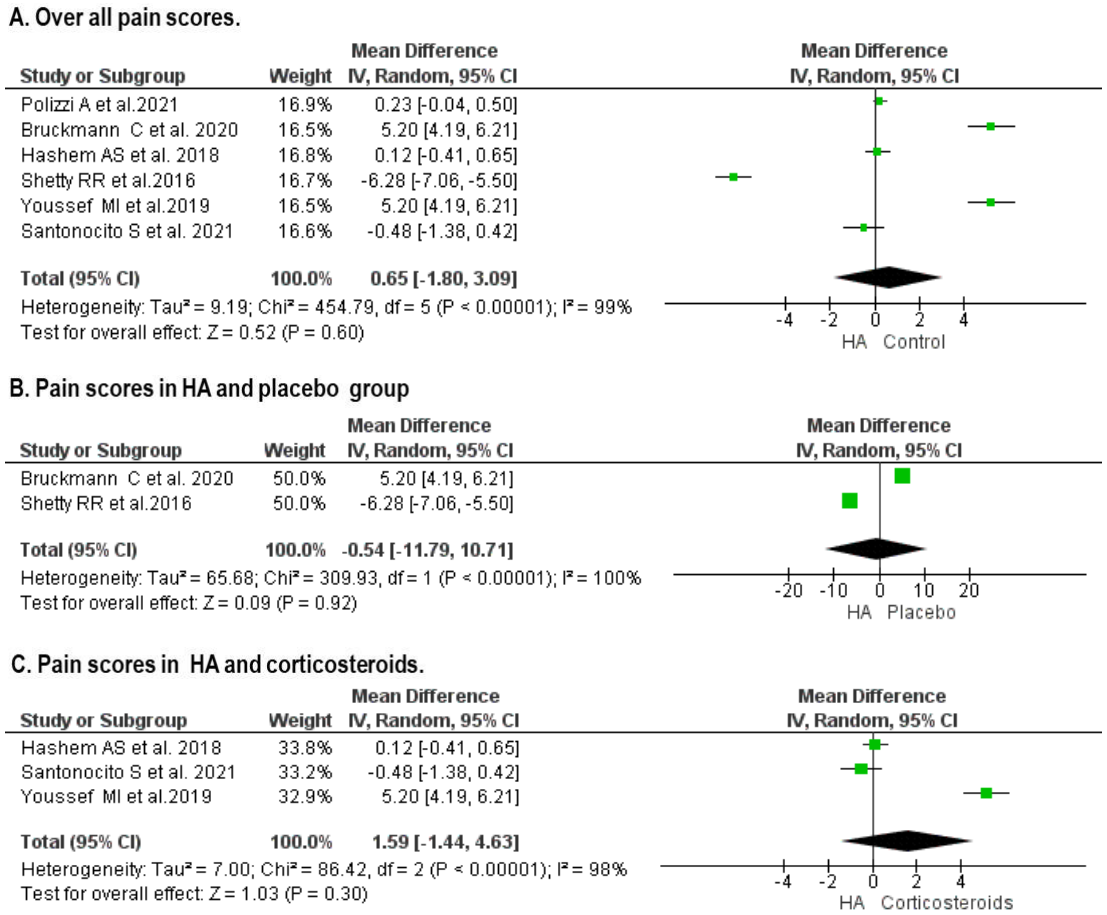

Fig. 3. Forest plot of comparison of the pain score. CI, confidence interval; HA, hyaluronic acid; IV, inverse variance.

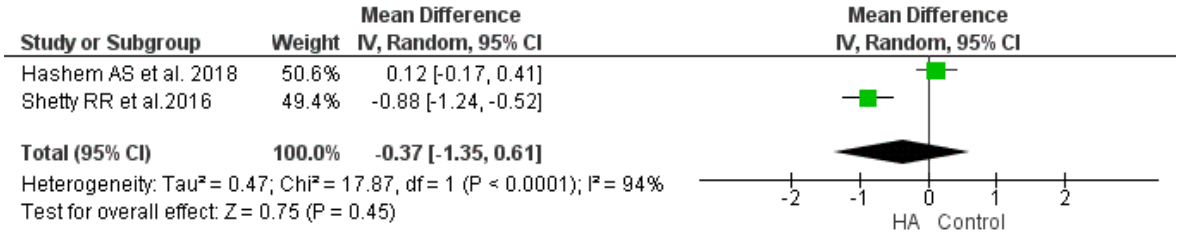

Fig. 4. Forest plot of comparison of the degree of erythema. CI, confidence interval; HA, hyaluronic acid; IV, inverse variance.

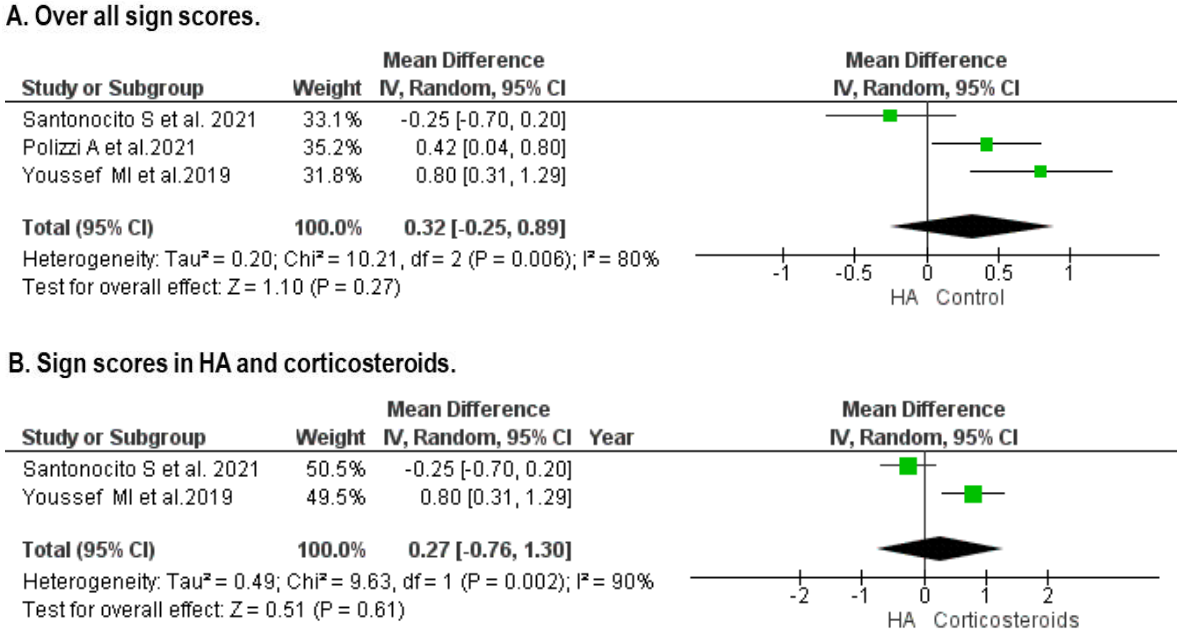

Fig. 5. Forest plot of comparison of the sign score. CI, confidence interval; HA, hyaluronic acid; IV, inverse variance.

Three studies (96 participants) compared the sign scores [13,19,20]. The pooled overall mean difference was 0.32 [95% CI: -0.25 to 0.89], which was not statistically significant (Z = 1.10, P = 0.27). High heterogeneity (I^2 = 80%, P = 0.006) was observed among the studies (Fig. 5A). The subgroup meta-analysis comparing HA with corticosteroid treatment from the two studies yielded statistically non-significant results (Z = 0.51; P = 0.61). (Fig. 5B) One study reported that both HA and tacrolimus were effective in reducing signs of OLP [19].

Only two studies qualitatively analyzed the clinical/disease severity index/scores [15,19]. The results were contradictory. In an RCT study, tacrolimus-treated OLP lesions showed a statistically significant improvement in disease severity scores. (P = 0.041) [19]. However, another RCT found no statistically significant difference between HA and placebo in terms of clinical severity index improvement [15].

DISCUSSION

To our knowledge, this is the first meta-analysis to assess the effectiveness of HA in OLP management. The present systematic review found that the lesion size, pain scores, degree of erythema, and Thongprasom sign scores in OLP were similar with respect to treatment with HA, corticosteroid, and placebo. The overall quality of evidence pertaining to Tacrolimus was moderate to low. Five studies reported a high risk of bias arising from one or more factors owing to bias in performance/

detection/attrition/reporting [6,14,15,18,19]. Two other studies reported an unclear risk of bias in selection/performance/detection [13,20]. A previous systematic review reported that three out of four studies showed a high risk of bias, while the present study also reported a high risk of bias in five out of seven studies [21]. Al Maweri et al. [21] followed the CONSORT guidelines to assess the quality and risk of bias of the included studies. The study by Nolan et al. [14] reported low risk, but in our study, we reported some concerns in the quality due to randomization, allocation, and reporting biases based on the Cochrane Risk of Bias tool [21].

The primary symptom that OLP patients report to clinicians is pain associated with the lesions. The correlation between a scoring system and referred pain is fundamental because OLP is considered a chronic condition [23]. In fact, patients affected by OLP usually experience pain only in some phases of the disease, followed by periods of remission. Validated scoring scales to assess symptoms in patients with OLP can range from VAS, numeric rating scale, change in symptom scale, or modified oral mucositis index [24]. Most of the studies used the VAS scale [6,13,15,18,20] except for Polizzi et al. [19] as they used the symptom score method reported by Raj et al. [25] In another study, the modified oral mucositis index was used [6]. Since different scales for pain assessment are used, the comparison between the different studies is difficult. Hence, it is necessary to establish an ideal scale and method to assess pain in such lesions.

A frequently used scoring system to grade the severity of OLP was developed by Thongprasom et al. [23] based on the presence and extent of white striae, erythema, and atrophy. Two studies used the Thongprasom scale [13,20], whereas Pollizi et al. [19] used the scale reported by Kaliakatsou et al. [26] which is modified from the Thongprasom scale. This could have resulted in methodological differences and affected the results. Different studies have used different methods to measure the lesion size [6,14,18]. Shetty RR et al. [6] used a flexible transparent sheet (intraoral grid) and calculated the area of the lesion. In studies by Nolan et al. [14] and Hashem et al. [18] the size was calculated using the maximum dimension of the lesion using calipers. Few studies have not measured the size of OLP lesions [13,15,20]. Moreover, different scales were used to measure disease severity. Pollizi et al. [19] used the disease severity score reported by Singh et al. [5] which involves a combination of both OLP symptoms and sign scores in an equally weighted manner, such that a total score of 5 (moderate disease) can be reached through a combination of 3 (signs) + 2 (symptoms) or 2 (signs) + 3 (symptoms), while Bruckmann et al. [15] used the clinical severity index. Therefore, a meta-analysis could not be performed for this parameter because of the lack of standardized methods.

In OLP, there is usually a constant presence of the lesions; however, the lesions do not remain in one area of the mouth and tend to migrate over time. The lesions are characterized by periods of exacerbation and quiescence [4]. Therefore, the follow-up of OLP forms an essential criterion to assess the response to treatment on a long-term basis. All included studies had different follow-up periods ranging from 1 month [6,14,18] to 3 months [13,19,20]. Assessing the nature and course of this disease is a long-term process that requires a deeper understanding of its pathogenesis and reasons for flares. Few authors have attempted to assess the response to treatment by assessing the downstaging of lesions using various methods [13,19,20]. One study used the pre-operative and post-operative Thongprasom scale [20] while in a study by Pollizi et al. [19] the preoperative and postoperative scores of symptoms and signs were compared. In a study by Youssef et al. [13], the VAS was used to assess the downstaging of lesions.

Another important point to be analyzed is that all studies used different controls in alongside to HA. In a few studies, corticosteroids were used as controls [13,18,20]. In other studies, placebo was used [6,14,15]. In a study by Pollizi et al. [19] Tacrolimus was used. Most of the studies [6,13-15,18] have used 0.2% topical HA, except for Pollizi et al. [19] and Santonocito et al.

[20] who have combined HA with anti-inflammatory agent (umbelliferone) and used as a mouth wash.

All the included studies were randomized controlled trials, except for the study conducted by Bruckmann et al. [15] which had a crossover RCT study design. The cross-over study design offers an advantage in that there is a reduced influence of confounders since patients serve as their own controls, and there is a reduced variability in the outcome(s) being measured, thus increasing the precision of estimation and a smaller sample size [27].

Few studies mention that transient improvement in clinical severity is seen in patients treated with HA [15,18]. This could be related to the anti-inflammatory effect of HA [15,20]. HA provides faster pain relief than corticosteroid ointment, irrespective of ulceration stage, and is associated with a lower risk of complications, discomfort, and drug interactions [11,12]. In a study by Santonocito S et al. [20] though HA showed limited ability in remission of signs of the lesion, no adverse or side effects or recurrences of the lesions treated by HA gel / ointments were reported upto 3 months, whereas minor gastrointestinal symptoms (22.22%), hypersensitivity to active drug, spontaneous bleeding, and fungal super infections were reported for the clobetasole group. In addition, Polizzi et al. [19] reported no side effects of HA mouthwash compared with tacrolimus. In this context, it is important to consider the potential side effects and uncertain clinical outcomes associated with the use of tacrolimus or corticosteroids, particularly in immunocompromised individuals or in patients with systemic illnesses in whom corticosteroids are contraindicated. In such situations, HA can be considered a beneficial alternative treatment.

The lack of a standardized protocol for measuring the clinical parameters related to the regression of OLP lesions was a major drawback in the included studies. The limited number of clinical trials and differences in the assessment of lesions using varied parameters could have contributed to the difficulty in arriving at a conclusion. Variations in sample sizes among various studies could have also resulted in bias. Long-term studies with larger sample sizes and evaluation of the ideal composition and concentration of HA are needed. Standardized methods for evaluating the severity of the disease, criteria for determining the levels of improvement, and patient-centered outcomes should be established. In addition, a longer follow-up period could make it easier to assess the frequency of relapses of OLP lesions and determine the therapeutic benefits of the protocols adopted in the long term.

CONCLUSION

The results showed that corticosteroids, placebo, and HA can be equally effective in the management of OLP. Similar reductions in lesion size, degree of erythema, pain scores, and sign scores were observed. The clinical/disease severity index or score reduction cannot be determined with sufficient certainty. Considering the anti-inflammatory effect and lack of side effects associated with its use, HA could be utilized as an alternative therapy in the treatment of OLP. The results should be interpreted with caution, as no definitive conclusions can be drawn owing to the limited number of clinical studies on HA, the high/unclear risk of bias, and the higher inconsistency of the included studies.

AUTHOR ORCIDs

Manjushri Waingade: https://orcid.org/0000-0002-1996-573X
Raghavendra S Medikeri: https://orcid.org/0000-0002-7879-8644
Shamali Gaikwad: https://orcid.org/0000-0002-0035-7021

AUTHOR CONTRIBUTIONS

Manjushri Waingade: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing

Raghavendra S Medikeri: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing

Shamali Gaikwad: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Software, Writing - original draft

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