Review Article

Evidence-based effectiveness of Ozone therapy in the treatment for oral lichen planus – A systematic review

ABSTRACT

Oral lichen planus is a common, chronic mucocutaneous condition of uncertain origin. Early treatment of OLP can dramatically reduce the risk of further development, which in turn reduces the risk of developing cancer. Numerous methods can be used to treat OLP. Since the significance of ozone in treating this disease is still uncertain. This systematic review was conducted based on english databases, including PUBMED, SCOPUS, Embase, Ovid, and Journal of Web up to July 2022. We used the search phrases "ozone," "ozone in the treatment of oral lichen planus," "oral lichen planus," and "ozone therapy." Finally, five papers were selected for qualitative analysis. This review included a total of five papers, four of which were clinical trials and one was a longitudinal study. All studies included the erosive form of OLP, also ozone therapy was applied to patients who did not respond to conventional treatment. Ozone showed significant therapeutic effects in terms of reduction in pain and size of the lesion. The signs and symptoms associated with OLP such as burning sensation, lesion size, and scarring all considerably improved with ozone therapy.

Keywords: Malignant transformation in OLP, oral lichen planus, ozone

INTRODUCTION

OLP continually impact the oral mucosa and disturb 1-2 percent of the general population.[1] In comparison to 25% of patients who only had oral lesions, nearly 50% of patients had mouth lesions in addition to skin lesions.[2] According to one definition of oral lichen planus; it is an "immunologic inflammatory mucocutaneous condition that can appear keratotic, erythematous, or ulcerative".[3] These lesions show a unique striae of white or gray line or dots on their surfaces. Louis Frederic Wickham in 1895 describes there striae in detail more clearly and coined the term "Wickham striae" for them.[4] The several OLP treatment options include medication, surgery, combination therapy, and low level laser therapy. Several drugs that have been proposed for these diseases are corticosteroids, collagenase, levamisole, pentoxifylline, curcumin, and antioxidants.[5] Ozone was 1st used in dentistry and medicine by Dr. C. Lender in 1870 disinfect blood in test tubes.[6]

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MATERIALS AND METHODS

Protocol

This study followed the PRISMA checklist, which is used to publish systematic reviews and meta-analyses (Moher *et al.* 2009).[7] The review was also registered under PROSPERO with registration number CRD42023389979.

Eligibility criteria

The study question was made more specific using the "PICOS" guideline. The research question was used to define the inclusion and exclusion standards.

- Population – Male or female patient with a clinically and histopathologically confirmed diagnosis of oral lichen planus.
- Intervention – Intraoral topical ozone therapy in the form of Ozonated water/Gas or oil.
- Comparison – The comparison group consisted of OLP treated by any other drug modality.
- Outcome - The major outcomes examined were a burning sensation on the VAS score and Improvement in the extent of the lesion.
- Setting – Private practice, health center, or cases in the general population.
- Exclusion criteria – Animal studies, editorials, and articles in other languages were excluded in our analysis.

Search Strategy/data source

This systematic review was based on English databases, including PUBMED, SCOPUS, Embase, Ovid, and Journal of Web up to July 2022. EBSCO was used for every search. We verified all relevant documents that were found using fully acquired electronic and other search tools. Unpublished research was obtained through conference proceedings and abstract searches. Databases were searched using keywords like Ozone or oral lichen planus or malignant transformation of oral lichen planus and ozone therapy.

SEARCH RESULTS

Searches in PubMed, Scopus, and Web of Science came up with a total of 11 articles. After the removal of studies that did not meet eligibility requirements and duplicate articles, 5 articles were selected for this study. Thus finally, five papers were evaluated of which four studies randomized clinical trials[8-11] and one was longitudinal study.[12] Detailed study and specific data are given in Tables 1 and 2. Figure 1 displays the information on articles included in PRISMA format.

The pain was the main factor that was evaluated in each case and was evaluated using the Visual Analog Scale (VAS Scale). Although Kumar T *et al.*[12] study omitted a control group. Veneri F *et al.*,[8] Mostafa B *et al.*,[9] Shete A *et al.*[10] and Kazancioglu HO *et al.*[11] included one that received steroid treatment. Mostafa B *et al.*[9] conducted the study, combining topical steroid application and ozone application. According to published studies, ozone therapy was applied after previous treatments had failed to make a difference, i.e., the OLP was not responsive to other interventions. Based on the study results, intra orally combined topical ozone treatment and topical steroid dramatically decreased pain scores in clinical trials, and a clear reduction in pain and ulcerative lesions, size of healing and when used separately single ozone therapy or topical steroid did not give a good result.[9]

Quality assessment and Evidence assessment/Risk of bias assessment

The quality of the included studies was rated separately for clinical trials and longitudinal study. The Cochrane risk of bias tool [Table 3][13] and JBI critical [Table 4] appraisal[14] were used to evaluate clinical studies and evaluation of longitudinal study respectively.

DISCUSSION

Lichen planus is a chronic inflammatory mucocutaneous condition that frequently impacts the oral mucosa and affects 1-2 percent of the general population.[2] It is believed to affect persons in their middle years (30 to 60 years old), with a 2:1 ratio of females to males. Induced apoptosis of basal keratinocyte is one of the fundamental causes. An underlying immune system dysfunction is seen in CD8+ T cells. Several signs of the condition are frequently present. Most of the lesions are bilateral and symmetrically distributed. The six clinical classifications defined by Andreasen in OLP can present in several ways, including reticular, erosive, atrophic, plaque-like, bullous, and erosive-ulcerous (erythematous).[2]

Ozone is a layer of defense that exists in the environment. It shields living things from the damaging effects of UV light. Ozone was discovered in 1839 by Christian Friedrich Schonbein which was then employed for practical uses and research in the fields of medicine and dentistry.[1] Many treatment modalities have been researched and published in previous kind of literatures with ozone, the use of ozone to treat oral lesions and persistent periodontal diseases was initially proposed in 1933.[4] Ozone is a potent oxidizing agent that can directly kill microbes and create free radicals, giving it antibacterial, antifungal, and antiviral properties. Ozone also promotes tissue repair and improves blood circulation. Ozone can be administered intravenously to treat conditions such as chronic periodontitis, caries, infections following dental extractions, radiotherapy-induced lesions, aphthae, and mycoses, as well as a disinfectant/irrigant in a root canal therapy.[1-4]

Table 1: Study of included possible clinical studies

Author	Study groups (No of participants)	Intervention preparation/ dose	Disease	Duration (months)	Follow-up months	Variables evaluated	Outcome
Veneri F *et al*. 2020[8]	51 patients Group A 26 Patient Group B 25 Patient	Group A Ozonized water treatment Betamethasone sodium phosphate 500 mg soluble tablets. Group B Placebo treatment i.e double distilled water Betamethasone sodium phosphate 500 mg soluble tablets.	Erosive OLP	24	3	Clinical erosive form Symptomatic lesions Burning sensation Pain	Group A Improvement in clinical signs. Reduction in pain and size of lesions. Higher efficacy index and less relapse rate. Group A&B Reduction in signs, pain scores, and size of lesions was seen.
Mostafa B *et al*. 2018[9]	66 pt. Group A 22 pt. Group B 22 pt. Group C 22 pt.	Group A STEROID Topical Triamcinolone Acetonide 0.1% four times/ day for four weeks. Group B OZONE Intraoral topical ozone with an intensity of 60% for 1 minute twice a week for 4 weeks. Group C STEROID+OZONE Combined Group Both topical (ozone& Steroids) application (twice weekly) followed by (four times daily) for four weeks with at least 2 hours intervals between topical ozone and steroid application	Atrophic erosive OLP Pain	Group A 4 weeks Group B 4 weeks Group C 4 weeks	5 Week	Burning sensation Pain Erosion	Pain scores decreased Group A Significant in steroids (p=0.0001) Group B The ozone group was not statistically significant (p=0.07) Group C Combined group (p=0.0004)
Shete A *et al*. 2017[10]	23 patients With OLP (Split mouth) Group A 23 patient Group B 23 patient	60 lesions of OLP were treated. Lesions on the right side were treated with a topical corticosteroid (control) and lesions on the left side were treated with ozone gas.	bilateral oral reticular lichen planus	Group A 3 weeks Group B 3 weeks	Both Group 1,3 & 6 months	Pain or Burning sensation in VAS Reduction in erythema present/absent Reduction in the size of lesions %	100 percent reduction in the size of the lesion 100% reduction in the size of the lesion absence of erythema with treatment group (Ozone therapy)
Kazancioglu HO *et al*. 2015[11]	60 patients With OLP (Split mouth) Group A 30 patient Group B 30 patient	Lesions on the right side were treated with a topical corticosteroid (control) Lesions on the left side are treated with ozone gas.	Patients with bilateral oral reticular lichen planus	Group A 3 weeks Group B 3 weeks	1, 3, & 6 months	Reticular, erosive, and atrophic lesions	Absence of erythema, VAS score 100% reduction of lesion size at 6 months with treatment group (Ozone therapy).

Table 2: Longitudinal study

Author	Study groups (No of participants)	Intervention preparation/dose	Disease	Duration (months)	Follow-up months	Variables evaluated	Outcome
Tarun Kumar *et al*. 2022[12]	50 patients (20-Oral candidiasis 10-Angular cheilitis 10-Aphthous ulcerations, 05-Oral lichen planus and 05 Herpes labialis)	Ozonized olive oil was applied topically	Oral candidiasis Angular cheilitis Aphthous ulcerations Oral lichen planus and Herpes labialis	Maximum of 6 months	1 Year	signs and symptoms	Improvement in the signs and symptoms in oral lichen planus patients.

Increased generation of cytokines that have immunomodulatory effects is associated with ozone treatment. By administering ozone treatment to patients with immunological conditions, there is elevation in the levels

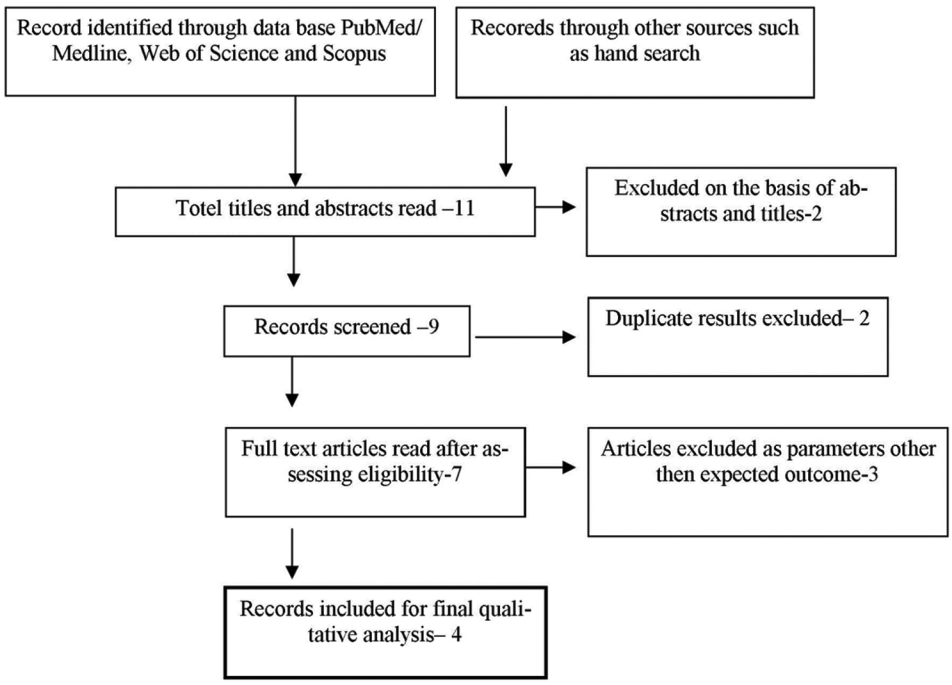

Figure 1: Flow chart diagram for article inclusion

Table 3: Cochrane risk of bias tool

Study ID	Selection bias		Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias	Other bias
	Random Sequence Generation	Allocation concealment	Selective reporting	Insufficient information	Blinding (participants and personnel)	Blinding (outcome)		
Veneri *et al*. 2020[8]	*	NA	*	*	**	*	*	*
Mostafa B 2018[9]	*	?	*	?	**	*	*	*
Shete A *et al*. 2017[10]	?	NA	*	*	**	*	*	*
Kazancioglu HO *et al*. 2015[11]	*	NA	*	*	**	*	*	*

* =Low risk; ** = High risk; ?= Uncertain risk

of interleukin 2 and gamma-interferon. These proteins are thought to be important in tissue regeneration and reversing immunological expression.[15] Since, OLP is an immunological disorder; it may be managed with ozone by this theory.

Topical Clobetasol propionate, Fluocinolone Acetonide, and Intralesional steroids such as Dexamethasone, or Triamcinolone acetonide, are the most preferred treatment modality but these medications have questionable results especially in advanced cases.[16] Therefore, there is a need for an alternate therapy approach that offers hope for success while having fewer side effects.

Recent studies have revealed that low O_3 concentration activates nuclear transcription and cell protective mechanisms without damaging cell structure or affecting cell growth. Ozonized water or olive oil was chosen as the formulation because it solves the problems associated with gaseous ozone, such as gas dispersion, inhalation toxicity which is very dangerous, and loss of local efficacy.[17,18]

Management of erosive oral lichen planus might be challenging but Ozone is efficient in treating OLP when given in reasonable doses for either a short or long period.[18] The known side effects include epiphora, upper respiratory tract irritation, rhinitis, coughing, migraines, rarely nausea and vomiting, shortness of breath and enlarged blood vessels. In care of ozone poisoning, the patient has to be given vitamin E and n-acetyl cysteine and should be placed in the supine position.[10]

Only those publications that analyzed oral lichen planus patients receiving ozone formulations with combinations and placebo groups were included in the analysis to lessen heterogeneity. The research did not use a uniform method

Table 4: JBI Critical appraisal

Components	Tarun Kumar *et al*. 2022[12]
1. Were the patient's demographic characteristics clearly described?	YES
2. Was the patient's history clearly described and presented as a timeline?	YES
3. Was the current clinical condition of the patient on presentation clearly described?	YES
4. Were diagnostic tests or assessment methods and the results clearly described?	YES
5. Was the intervention (s) or treatment procedure (s) clearly described?	YES
6. Was the post-intervention clinical condition clearly described?	YES
7. Were adverse events (harms) or unanticipated events identified and described?	YES
8. Does the case report provide takeaway lessons?	YES

for diagnosing oral lichen planus; therefore certain aspects of variability cannot be ignored. Additionally, the follow-up period for each outcome examined was not the same length of time.

In recent years, ozone therapy as an additional treatment for OLP has attracted a lot of interest. To the best of our knowledge, this is the first systematic review on OLP and ozone because the body of literature is so sparse. The main emphasis of treatment for OLP is to regulate and reduce inflammation because it appears to be an incurable disorder. Numerous interventional techniques have been used, including topical and systemic steroids, retinoids, calcineurin inhibitors, phototherapy, lasers, immunosuppressants, curcumin, aloe vera and Platelet-rich plasma protein.[16,19] However, OLP instances seem to be resistant compared to all.[4,16]

There is still no known long-term treatment. Furthermore, these interventional techniques have a history of negative outcomes, which restricts their application in OLP in patient with blood pressure, blood sugar, and gastrointestinal disease.[4,16] Therefore, ozone intervention looks to be a promising modality for treating OLP due to its low cost and efficacy. Ozone does seem to be effective in oral lichen planus, but still, further research in this arena is needed by using a large sample size with specific protocols and standard methods of evaluation.

CONCLUSION

Promising results should inspire a larger clinical trial with more OLP patients to expand the therapeutic use and applicability of ozone. This baseline study paves the way for more researches into the application of ozone alone in the treatment of OLP.

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Conflicts of interest

There are no conflicts of interest.

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