



FACULTAD DE CIENCIAS DE LA SALUD

CARRERA PROFESIONAL DE ESTOMATOLOGÍA

**“El aceite ozonizado en el tratamiento de lesiones orales: una
revisión sistemática”**

Tesis para optar el grado académico de:

MAESTRO EN PERIODONCIA E IMPLANTES

Presentado por:

Jusef Yábar Condori (0000-0003-2932-9849)

Asesor:

Gerardo Mendoza Azpur (0000-0002-6548-1285)

Lima – Perú

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ACTA DE SUSTENTACIÓN DE TESIS

Lima, 30 de Setiembre de 2021.

Los integrantes del Jurado de tesis:

Presidente: Mg. Erick Gianmarco Valdivia Frías	<input type="checkbox"/>
Miembro: Mg. Andrea Victoria Vergara Buenaventura	
Miembro: Dra. Myriam Angelica de la Garza Ramos	

Se reúnen para evaluar la tesis titulada: **“EL ACEITE OZONIZADO EN EL TRATAMIENTO DE LESIONES ORALES: UNA REVISION SISTEMATICA”**

Presentada por el estudiante/bachiller:

- C.D Jusef Yabar Condori

Para optar el Grado Académico de Maestro en Periodoncia e Implantes

Asesorado por: Mg. Gerardo Mendoza Azpur

Luego de haber evaluado el informe final de tesis y evaluado el desempeño del estudiante de la Carrera de Estomatología en la sustentación, se concluyen de:

Manera unánime (X)

Por mayoría ()

Calificar a:

Tesis: Jusef Yabar Condori		Nota (en letras): Quince	
Aprobado (X)	Aprobado - Muy buena ()	Aprobado- Sobresaliente (X)	Desaprobado ()

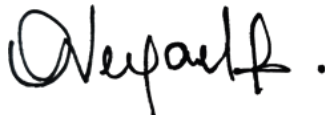
Los miembros del jurado firman en señal de conformidad.



Mg. Erick Gianmarco Valdivia Frías
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Dra. Myriam Angelica de la Garza Ramos
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UNIVERSIDAD CIENTÍFICA DEL SUR
POSGRADO ESTOMATOLOGÍA

INDICAR EL TÍTULO DE SEGUNDA ESPECIALIDAD O GRADO ACADÉMICO A OPTAR
DECLARACIÓN DE ORIGINALIDAD DE CONTENIDO DE INFORME FINAL DE TESIS¹³

Lima, 19 de octubre del 2023

Señor:

Carlos Zavalaga Reyes

**Director General de Investigación, Desarrollo e Innovación
Universidad Científica del Sur**

Presente.-

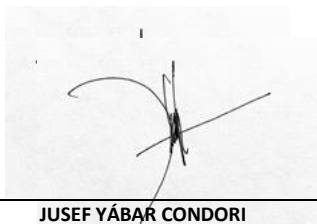
De nuestra consideración,

Yo: Jusef Yábar Condori, egresado del Posgrado Estomatología de la Universidad Científica del Sur, en conjunto con el asesor de tesis Gerardo Mendoza Azpur, declaramos que este informe final de tesis titulado: ¿El uso del aceite ozonizado es efectivo en el tratamiento de lesiones orales? Revisión sistemática de estudios clínicos, sustentado para obtener el Grado Académico de Maestro en Periodoncia es original.

Es decir, no contiene plagio parcial ni total, cuando se utilizó información de fuentes externas se reconoció la autoría mediante la adecuada citación y los resultados obtenidos son producto entero de mi (nuestra) investigación y no han sido falseados ni fabricados. Todo esto en cumplimiento del Código de ética en la investigación, Reglamento del Comité de Integridad Científica, Reglamento de Propiedad Intelectual, Normas y procedimientos de los trabajos de investigación para la obtención de títulos profesionales y grados académicos¹⁴, que afirmamos conocer en su totalidad.

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JUSEF YÁBAR CONDORI
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GERARDO MENDOZA AZPUR
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¹³ En conformidad con la Resolución del Consejo Directivo N° 084-SUNEDU/CD

¹⁴ Los documentos están en: <https://investigacion.cientifica.edu.pe/reglamentos/>

INFORME DE REVISIÓN DE ORIGINALIDAD

Título del documento evaluado. El aceite ozonizado en el tratamiento de lesiones orales: una revisión sistemática

Autores. Josef Yabar Condori

Mecanismo de revisión de originalidad. Evaluación con Turnitin (ID 2294174693).

Resultado de la evaluación. 9%

Revisado por. Magaly Kelly Guerrero Huaracallo.

Comentarios sobre la revisión. Filtros usados: excluir fuentes de menos de 12 palabras.



DEDICATORIA

Este trabajo se los dedico a mis hijos Rafael, Francisco y a mi esposa Bertha, que son mi inspiración para crecer cada día y ser cada vez mejor.

RESUMEN

El objetivo de este estudio fue realizar una revisión sistemática (RS) del efecto terapéutico del aceite ozonizado sobre las lesiones orales. Se realizó una RS siguiendo las directrices PRISMA. Se realizaron búsquedas en Medline (PubMed), Embase, Cochrane Library, Scielo y LILACS, y búsquedas manuales, que abarcaron hasta diciembre de 2020, de ensayos clínicos aleatorizados y no aleatorizados que informaran sobre el efecto de los aceites ozonizados en el tratamiento de las lesiones orales en comparación con cualquier otro método. El riesgo de sesgo (RoB) de los estudios incluidos se evaluó mediante la herramienta RoB 2 y ROBINS-I. Tras analizar los títulos y leer los resúmenes, se excluyeron 1932 artículos; los 25 restantes pasaron una evaluación exhaustiva del texto completo. Finalmente, se incluyeron 13 artículos en esta RS. Hubo heterogeneidad de resultados en cuanto a los tiempos de cicatrización y los intervalos de aplicación del aceite ozonizado para el tratamiento de cada tipo de lesión oral, pero en general, hubo un menor tiempo de cicatrización cuando se utilizó el aceite ozonizado como terapia, y no se comunicaron efectos adversos. A pesar de la limitada información encontrada y de la falta de normas metodológicas rigurosas sobre el uso de aceite ozonizado en lesiones orales, se sugirió un efecto positivo del uso de aceite ozonizado para el tratamiento de lesiones orales. Los resultados indicaron una ventaja en términos de menor tiempo de curación en comparación con otros tratamientos convencionales; además, no se notificaron efectos adversos, por lo que se demostró una opción de tratamiento segura y fiable para los pacientes.

Palabras claves: Boca; Ozono; Terapéutica; Heridas y lesiones

ABSTRACT

The aim of this study was to perform a systematic review (SR) of the therapeutic effect of ozonated oil for oral lesions treatment. A SR was conducted according to the PRISMA guidelines. The Medline (PubMed), Embase, Cochrane Library, Scielo and LILACS were investigated, together with manual searches, to extract all publications until December 2020, including randomized and non-randomized clinical trials reporting the effects of ozonated oils on the management of oral lesions when compared with other methods. The risk of bias (RoB) of the studies included were assessed by using the RoB 2 tool and ROBINS-I. After analyzing the titles and reading the abstracts, 1932 articles were excluded; the remaining 25 passed a full-text evaluation. Ultimately, 13 articles were included in this SR. There was heterogeneity of the results regarding healing times and intervals of ozonated oil application for the treatment of each type of oral lesion, but in general, there was a shorter healing time when ozonated oil was used as therapy, and no adverse effects were reported. Despite the limited information found and the lack of rigorous methodological standards for the use of ozonated oil on oral lesions, a positive effect was suggested. The findings indicated an advantage in terms of shorter healing times when compared with other conventional treatments. No adverse effects were reported, showing safety and reliability for patient's treatment.

Keywords: Mouth; Ozone; Ozoile; Therapeutics; Wounds and injuries.

VERSIÓN APROBADA PARA PUBLICAR**I. INTRODUCTION**

Oral mucosa lesions could be presented as changes in color, appearance, swelling or loss of the integrity of the tissue surface. Some types of these lesions may be benign and do not require any treatment, others may present acute symptoms, affecting patient's quality of life, causing difficulties with swallowing and speech, with symptoms such as burning, irritation and pain (1). The prevalence of oral lesions in the general population worldwide ranges from 4.9% to 64.7% (2, 3).

The oral mucosa could be an easily accessible point of entry for infectious agents, such as bacteria or viruses. Therefore, an early diagnosis and treatment is essential to avoid future complications or the development of serious, even malignant lesions (4). There are several alternatives for conventional treatment according to the type of mucosal lesion the patient has, however, some of these have been shown to be inefficient, by generating discomfort to the patients and requiring relatively extended treatment times. In view of the foregoing, there are treatment alternatives in natural and traditional medicine that are used as therapy for oral diseases, such as ozone therapy that has shown some positive findings (5). Ozone is a natural gaseous molecule formed by 3 oxygen atoms. Ozone has been recognized for being immunostimulant, analgesic, anti-hypnotic, detoxifying, antimicrobial, and being capable of performing bioenergetic and biosynthetic actions. Due to its atraumatic, painless, non-invasive characteristics, it can be considered highly reliable and has shown a high acceptance rate among patients (6). There are 3 ways to apply ozone: ozone gas, ozonated water and ozonated oil (7).

Ozonated oil results from the reaction of ozone with fatty acids and other substances, by means of bubbling ozone through of a generator. During this reaction, substances such as peroxides, ozone, aldehydes and ketones are formed (8, 9). Ozonated oil that comes into contact with exudates or injuries is divided and generates ozone, releasing hydrogen peroxide and lipoperoxides, promoting regenerative and disinfectant effects. This slow release of ozone further promotes the healing process by acting as a local antimicrobial agent and promoting cytokine release with an effect on tissue repair (10).

There are many studies where ozonated oil has been used as a therapeutic agent for different types of oral lesions, showing better results than control conventional treatments. Some benefits described in the literature include quicker healing, less discomfort and absence adverse effects (5, 11-22). However, there is no standardized methods to apply it, benefits or the ideal treatment time. Consequently, a systematic review was realized to answer this focused question according to a PICO strategy: Is the use of ozonated oil effective in the treatment of ulcerated lesions of the oral mucosa? And: is the use of ozonated oil effective in the treatment of alveolar bone lesions?

II. MATERIALS AND METHODS

PROTOCOL AND REGISTRATION

This SR was carried out under the parameters of the Transparent Reporting of Systematic Reviews and Meta-Analysis-PRISMA Statement (23) and was registered at PROSPERO with number CRD42021237068.

FOCUSED QUESTION

The focused questions to be addressed were:

1. Is the use of ozonated oil effective in the treatment of ulcerated lesions of the oral mucosa?
2. Is the use of ozonated oil effective in the treatment of alveolar bone lesions?

ELIGIBILITY CRITERIA

The inclusion criteria for this SR were the following: Clinical studies that used ozonated oil as a treatment for different oral lesions (subprosthetic stomatitis, recurrent aphthous stomatitis, herpetic gingivostomatitis, pericoronaritis, alveolitis and fibroedematous gingivitis). Literature reviews, letters to the editor, short communications, case reports, pilot studies and trials that analyze other applications of ozonated acceptance not related to oral injuries were excluded.

SEARCH STRATEGY

The MEDLINE (PubMed), Embase, Cochrane Library, Scielo and LILACS databases were searched up to March 2021 by two independent reviewers (J.Y and J.A). The search was performed without restrictions on dates or language. The search strategy was applied as follows: PubMed: ("Aphthous stomatitis" OR "Dry Socket" OR "Pericoronitis" OR "Herpetic Stomatitis" OR "subprosthetic stomatitis" OR "fibro edematous" OR "alveolitis" OR osteomyelitis OR "Aphthous Ulcer" OR "Aphthous Stomatitides" OR "Alveolar Osteitis" OR "Herpetic Gingivostomatitis" OR "Oral Herpes Simplex" OR "oral injury" OR "oral lesion") AND ("ozonated oil" OR "Ozonated" OR "ozonation" OR "ozone" OR "Ozonized" OR "ozone therapy" OR "ozonotherapy" OR "ozonating" OR "oleozon" OR "vegetable oils" OR "plant oils" OR "ozonation"). Additionally, the grey literature were screened electronically in the System for Information on Grey Literature in Europe (<http://www.opengrey.eu>), as well as, Google Scholar databases, as recommended by the high standards for systematic reviews (AMSTAR guideline) (24). At the end, the list of references of studies included were also hand searched to find any potential additional records, as recommended by Greenhalgh and Peacock (25).

DATA COLLECTION, EXTRACTION AND MANAGEMENT

SCREENING AND SELECTION OF ARTICLES?

Two independent reviewers (JY. and JA) made screened of titles and abstracts. All the studies that seems to meet inclusion criteria, full- texts were obtained and then review. It was verifying the eligibility and level of agreement between the reviewers using the Kappa Score (Cohen's Kappa coefficient) during the full-text assessment. Disagreements were solved by discussion and consulting a third reviewer (GM).

DATA EXTRACTION

The studies that applied all criteria were processed for data extraction. The extraction was done using predefined spreadsheets by two independent researchers. Disagreements were resolved by discussion with a third reviewer. when there is missing data, it was sent an e-mail to the authors. For all the studies selected, the following variables were collected: 1) characteristics of the study: author, year of publication, country, design of the study (randomized clinical trial and non-randomized); 2) demographic data: sample size, mean age (years) and gender (male/female); 3) outcome measures: healing time, application interval and adverse effects (presence or absence).

RISK OF BIAS IN INDIVIDUAL STUDIES

Two reviewers (J.M.M and J.Y) evaluated the risk of bias in studies selected, using the Cochrane tool for risk of bias assessment, RoB 2 (version 2, available at: <https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2>).

The authors of this SR decided to evaluate the result related to "assignment to the intervention (the effect for the purpose of treating)" and five domains were examined: randomization bias and treatments concealment, bias due to deviations from the planned interventions that affected the involvement of the participants and a team of researchers, although there were missing result data, the result measurement and the result selection were selected. Based on the responses to the questions and the algorithms of the tool, it was considered that each domain had "low risk of bias", "some concerns related to risk of bias" or "high risk of bias". The studies were categorized as low risk of bias (all domains had low risk of bias), high risk of bias (one or more domains had high risk of bias) and

concerning (when one or more domains had some concerns) (26). The decisions were resolved by means of discussion, consulting a third advisor (G.M).

The non-randomized controlled trials were evaluated by means of the ROBINS-I tool. (27) Each controlled trial was classified as low information, or as low, moderate, severe and critical risk of bias. The discrepancies between the reviewers were resolved by means of open discussion. In the event that an agreement could not be achieved, the final decision was made by another co-author (G.M).

The following domains have evolved to not randomized controlled trials (27):

Preintervention

- Confusion bias

- Selection bias

Intervention

- Bias in the classification of interventions

Post-intervention

- Bias due to deviations from planned interventions

- Bias due to missing data

- Bias in the results measurement

- Bias in the selection of the informed result

To demonstrate the general risk of bias, each study included was classified as low, moderate, severe and critical risk of bias or the absence of information according to the following criteria:

- Low risk of bias: is considered to have a low risk of bias for all domains.
- Moderate risk of bias: is considered to have a low to moderate risk of bias for all domains.
- Severe risk of bias: is considered to have a severe risk of bias for at least one domain, but it does not have a critical risk of bias for any domain.
- Critical risk of bias: is considered to have a critical risk of bias in at least one domain.
- No information: there is no clear indication that the study has a serious or critical risk of bias and there is a lack of information on the most key domains for bias (a judgment is required for this).

III. RESULTS

STUDY SELECTION

The electronic search strategy identified 1957 articles. After analyzing the titles and abstracts, 1932 studies were excluded, the remaining 25 were subject of a full text exhaustive evaluation, from which 12 were excluded. As a result, 13 papers were included in this SR (Figure 1).

STUDY CHARACTERISTICS

The thirteen randomized (5, 11, 12, 14, 16, 18-20) and non-randomized clinical trials (13, 15, 17, 21, 22) included were done between 2010 and 2020, and their main methodological characteristics are presented in Table 1. All clinical studies showed the effective outcome of the ozonated oil on different types of oral lesions: subprosthetic stomatitis, recurrent aphthous stomatitis, herpetic gingivostomatitis, pericoronitis, alveolitis and fibro edematous gingivitis; and used as a control and conventional treatment for each type of oral lesion. A total of 1644 patients from different age groups were included in the present SR. Participants in 3 studies suffering from pericoronitis (11, 12, 22), participants in 3 studies developing alveolitis (5, 18, 22), 5 studies conducted in patients with recurrent aphthous stomatitis (14, 16, 19, 21, 22), 3 studies based on subprosthetic stomatitis (15, 17, 22), 2 studies were based on patients with fibroedematous gingivitis (20, 22), lastly a single study contemplating the use of ozonated oil for patients with herpetic gingivostomatitis (13). In all studies the local application of ozonated oil was used as therapy. The follow-up periods varied from 72 hours to 6 weeks, depending on the type of wound.

OZONATED OIL IN PERICORONITIS

In 2 randomized clinical trials (RCT) (11, 12) and 1 non-RCT(22) authors reported the use of the ozonated oil as therapy for pericoronitis and compared it with conventional therapy consisting of 50% trichloroacetic acid and mouthwashes with 0.2% chlorhexidine for a

period of time between 3 to 7 days, an interval of application was 3 to 4 times a day, with a healing time between 72 hours and 7 days, a larger number of patients recovered in less time in the study group (ozonated oil), while the control groups showed lower satisfaction rates in same period of time, showing statistically significant differences. No adverse effects were reported.

OZONATED OIL IN ALVEOLITIS

In 2 RCT (5, 18) and 1 non RCT (22) Ozonated oil treatment was used as a treatment for alveolitis and compared it with alvogyl. All the studies had a 7-day follow-up period, the time interval in which the healing took place. The lesions healing times were heterogeneous, varying between 4 days (18), 5 days (5) or up to 7 days (22) for study group (ozonated oil), the interval of application varied from 4 times a day (22) up to every 72 hours (5), no adverse effects were reported. In all cases, a shorter recovery time was observed when Ozonated oil was used as therapy. However, only one study (5) reported statistically significant differences.

OZONATED OIL IN FRIBROEDEMATOUS GINGIVITIS

Only 2 studies: 1 RCT (20) and 1 non-RCT (22), used the Ozonated oil therapy for fibroedematous gingivitis and it was compared with the use of chlorhexidine mouthwashes at 0.2%, the healing time varied between 7 days (22) showing only favorable results in study group (ozonated oil) and 6 weeks (20) (in which 96.6% of patients healed in the study group), the interval of application varied from 4 times a day (22) to 2 times a week (20), no adverse effects were reported. In both studies there was a shorter healing time when ozonated oil was introduced.

OZONATED OIL IN SUBPROSTHETIC STOMATITIS

Three (15, 17, 22) of the studies included in this SR (non-RCT) used ozonated oil as treatment for subprosthetic stomatitis and compared it with conventional treatment consisting of nystatin. The follow-up time ranged from 7 days (17, 22) to 15 (15), on the

other hand, the interval of application of ozonated oil for this type of injury varied from once a day (15, 17) to 2 times a day (22). The healing time found in the studies varied from 7 days (17, 22) up to 12 days (15). In all the studies, there was a shorter recovery time when Ozonated oil was used as therapy compared with treatment with nystatin. No adverse effects were reported.

OZONATED OIL IN RECURRENT APHTHOUS STOMATITIS

In 3 RCTs (14, 16, 19) and 2 non-RCT (21, 22) studies the Ozonated oil was used to treat recurrent aphthous stomatitis and compared it with other therapies such as: multivitamins and 0.2% chlorhexidine mouthwashes (14, 19), sodium perborate alkaline mouthwashes and 0.2% chlorhexidine mouthwashes (16, 22), and finally a comparative study with metronidazole gel (21), with a follow-up time ranging from 7 (14, 16, 19, 22) to 14 days (21), an interval of application of between 2 (14, 19, 22) to 4 (16, 21) times a day, as a healing time between 5 (14) and 7 days (16, 19, 21, 22). In all cases, a shorter recovery time was observed when Ozonated oil was implemented as therapy. Only 2 studies (19, 21) reported statistically significant differences. No adverse effects were reported.

OZONATED OIL IN HERPETIC GINGIVOESTOMATITIS

Only 1 non RCT study (13) included in the present SR used the Ozonated oil as therapy for herpetic gingivoestomatitis and compared it with the use of idoxuridine at 0.1% with a follow-up period of 10 days, the healing time was ≤ 8 days for the control group, the interval of application was once a day, without specifying the presence of the adverse effects. The patients treated with the Ozonated oil had a shorter healing time of the lesion.

RISK OF BIAS IN THE STUDIES SELECTED

In RCT studies, inadequate methods of generating sequences and assigning participants were found in all of the publications (90%) included and only one study showed a correct assignment process between groups (Figure 2). Among the deviations from the planned interventions, 60% of the studies were classified as "high" due to problems with the masking process (Figure 3). However, it was not possible to mask the entire staff due to

the experimental context. At the end, all studies showed results without a pre-specified plan. In general, it was considered that only one study had a clear risk of bias. Figures 2 and 3 show a summary of the results.

Three of the non-RCT studies were classified as having a severe risk of bias (15-17), one study with a moderate risk of bias (21) and one study was classified as having a critical risk of bias (13) as shown in Figure 4.

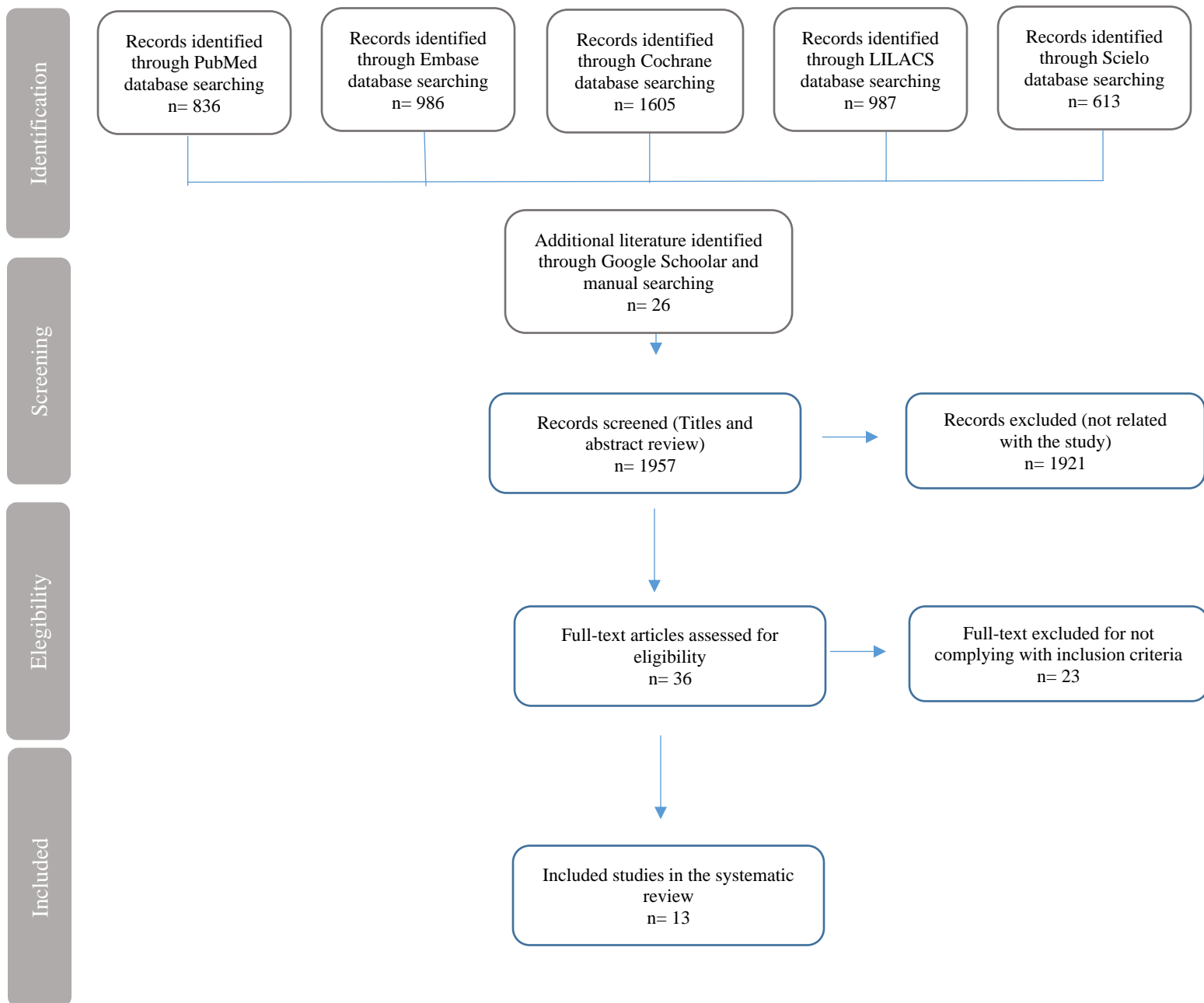


Figure 1. Flow chart of manuscripts selected through the review process.

	D1	D2	D3	D4	D5	Overall	
Peña et al; 2019	-	-	+	!	-	-	+ Low risk
Leal et al; 2019	-	-	+	+	!	-	! Some concerns
Souto et al; 2018	-	!	+	-	!	-	- High risk
Diaz et al; 2018	-	-	+	-	!	-	
Fontaine et al; 2016	-	+	+	-	!	-	D1 Randomisation process
Martinez et al; 2015	+	+	+	+	!	!	D2 Deviations from the intended interventions
Mayor et al; 2011	-	-	+	-	-	-	D3 Missing outcome data
Mayor et al; 2010	-	-	+	-	-	-	D4 Measurement of the outcome
							D5 Selection of the reported result

Figure 2. Risk of bias summary of the clinical trials, included in the systematic review, based on the Cochrane risk of bias tool, RoB 2.

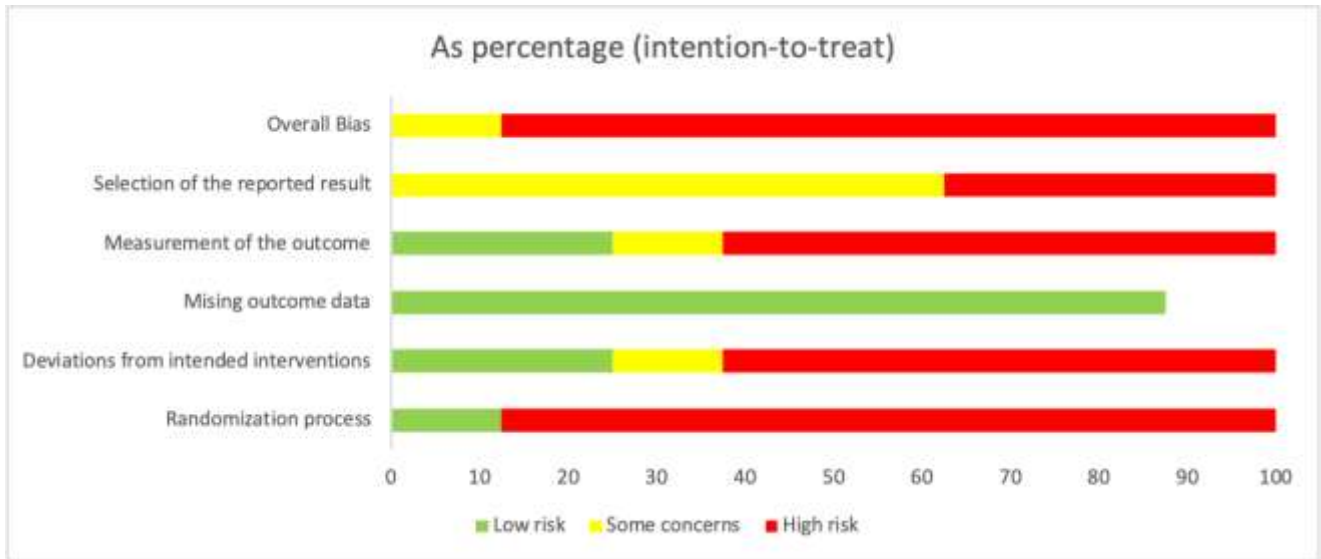


Figure 3. Risk of bias summary as a percentage of the clinical trials included in the systematic review.

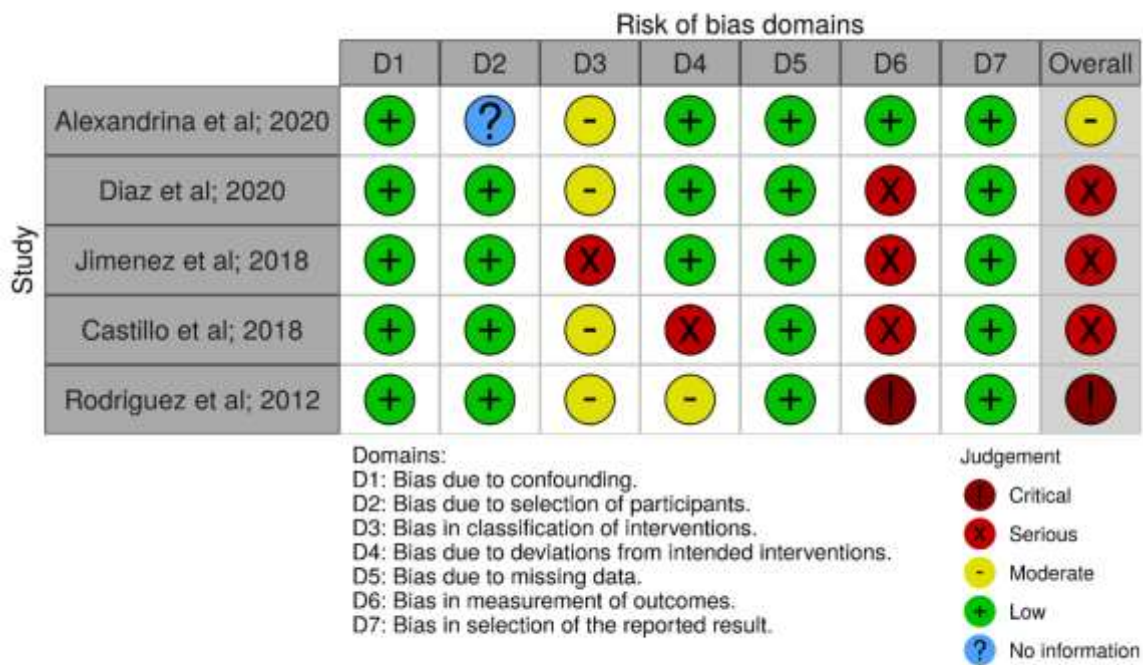


Figure 4. Risk of bias summary of the non-randomized clinical trials included in the systematic review, based on the tool ROBINS-I.

Table 1. Main characteristics of the included studies in the systematic review

Author and year	Design	N	Age	Gender (M/F)	Type of oral lesion	Test group	Control group (CG)	Assessed parameters	TF	AI	HT SG/CG	AE	Results
Mayor & col. ⁽¹¹⁾ 2010	RCT	90	> 15	25/65	pericoronitis		50% trichloroacetic acid	Clinical evaluation: satisfactory (improvement or cure at 72h), unsatisfactory (equal to or worse at 72h). Efficacy of the study drug: good (satisfactory clinical evolution), poor (unsatisfactory clinical evolution)	72h	3 times a day	72h/>72h	no	100% good efficacy for SG (OO), 62% good efficacy and 38% poor efficacy for CG (trichloroacetic acid).
Mayor & col. ⁽¹²⁾ 2011	RCT	90	> 15	Not specified	pericoronitis		50% trichloroacetic acid	Microbiological evaluation: satisfactory (field absent or scarce, Gram- not predominant), unsatisfactory (abundant field or covered field, Gram-predominate). Degree of patient satisfaction (satisfied vs not satisfied, according to the patient's appreciation) and adverse effects (yes or no)	72h	3 times a day	72h/>72h	no	Microbiological evaluation, satisfactory SG in 43 patients (96%), satisfactory CG in 18 patients (40%). Patient's satisfaction: Satisfactory SG 43 patients (96%), CG 30 patients (66%).
Rodriguez & col. ⁽¹³⁾ 2012	No RCT	250	<9	82/68	Herpetic gingivostomatitis		0.1% idoxuridine	Evolution: Cured: When there are no clinical signs of Acute Herpetic Gingivostomatitis. Not cured: When there are clinical signs of Acute Herpetic Gingivostomatitis in the oral cavity	10d	1 time a day	≤8d/8a/10d	no	79 patients treated with OO (63.2%) cured in < 6 days, 78 patients treated with idoxuridine (62.4%) were cured in 9 to 10 days; the treatment with OO minimized the healing time.
Martinez-Abreu & col. ⁽⁵⁾ 2015	RCT	100	20-59	56/44	Alveolitis		Alvogyl	Clinical: recovered (pain and inflammation disappear), improved (pain and inflammation decrease), the same (pain maintains intensity and inflammation persists), worse	7d	Every 72h	3 to 4 days/>3,4 days	Not specified	100 patients in 2 groups: 50 SG (OO) and 50 CG (alvogyl) The patients were evaluated at 72h (2nd visit), 96h (3rd visit) and at one week of treatment (4th visit). 41 SG patients only

Fontaine & col. (14) 2016	RCT	80	>12	26/54	recurrent aphthous stomatitis	vitamins and mouthwash with 0.2% chlorhexidine.	Ozonated oil	(pain and inflammation persists or worsens). Microbiological: infected (presence of mopyogens), free of infection (absence of mopyogens) Efficacy evaluation: good (clinical criterion of recovered and microbiological free of infection), acceptable (clinical criterion of improved and microbiological free of infection) and poor (clinical criterion of equal or worse and microbiological infected). Clinical evaluation: satisfactory (the pain decreases or disappears; the size of the lesion decreases or disappears) not satisfactory (the pain persists and there is no change in the lesion). Healing: cured (there are no clinical signs of stomatitis) and not cured (there are clinical signs of stomatitis in the mucosa). Degree of satisfaction: satisfied and not satisfied (for both criteria the perception of the patients was taken into account).	7d	2 times a day	4 to 5 days / >7 days	no	needed 2 visits to recover, CG only 29 patients. For the microbiological evaluation: From 20 patients in the SG 13 patients showed signs of recovery from infection, while in the CG from the 20 evaluated patients only 6 showed the same result. SG and CG 40 patients each. OS: 34 patients needed only two to three applications to consider a satisfactory clinical evaluation, 38 patients only needed a maximum of 4 to 5 days to consider themselves cured. CG: 18 patients needed more than 7 days. Degree of satisfaction: 97.5% of the GE satisfied.
Castillo & col. (15) 2018	No RCT	68	>19	17/51	subprosthetic stomatitis	nystatin	Ozonated oil	Clinical evaluation, healing was determined as the lesion disappeared and the physiological mucosa became	15d	1 time a day	4 to 12d / 7 to 15d	no	CG the mucosa recovered normality between 10 to 12 days (52.9% of the sample). Only 14.7% achieved it between 7 and 9 days; no patient was healed during the first

														week of treatment.
Diaz-Couso & col. (16) 2018	RCT	3 2	> 12	12/2 0.	recurrent aphthous stomatitis	Ozonated oil	alkaline mouthwashes sodium perborate and mouthwashes 0.2% chlorhexidine	Cured , there is a good general condition of the affected area (remission of symptoms) and disappearance of the ulcer. Not cured , permanence of the ulcer, the symptoms do not subside with the application of the medicine. For the criterion of adverse reactions, the presence in the affected area of burning, redness, heat, tumor and pain was taken into account.	7d	4 times a day	3 to 7 days on both groups	no	On the third day, the eight SG patients evolved favorably (50%) and in the CG it was 12.5%. In general the evolution of the treatment, cured patients: SG 93.7% and CG 68.7%.	
Jimenez & col. (17) 2018	No RCT	4 0	> 20	17/2 3	subprosthetic stomatitis	Ozonated oil	nystatin	Treatment effectiveness: Very effective, effective and not very effective.	7d	1 time a day	4 to 7 days / >7 days	no	Evaluation of the effectiveness of treatment in sub-prosthesis stomatitis: SG, effective treatment in 14 patients (35.0%), CG, ineffective treatment with 18 patients (45.0%). The daily application of OO was effective for the treatment of this disease between four and seven visits to consultation, healing time was shorter compared to	

Souto & col. (18) 2018	RCT	1 0 0	20- 59	Not spec ified	alveolitis	alvogyl	Pain (referred by the patient at the beginning and after the application of the treatments at 5, 15, and 30 minutes, visual analog scale) Inflammation (state of the mucosa surrounding the alveolus, by direct observation: inflamed (hyper-colored, increased in volume, smooth); slightly inflamed (slightly hyper-colored and slight increase in volume) and non-inflamed (normally colored, resilient and normal size). Scarring: non-healing (delayed clot formation, stench, hypersensitivity in the walls of the alveolus), partial scarring (despite the new clot formation, presents hypersensitivity, slight stench) and total scarring (alveolus occupied by a new blood clot) , with formation of granulation tissue and proliferation of the epithelium on the external surface). Response to treatment: no response to treatment (same patient , pain does not disappear, no clot formation, hypersensitive alveolus walls and stench), improved (not intense pain, slight stench and new clot formation) and	7d	1 applicat ion	4 to 5d/ >7 d	Not speci fied	nystatin cream in the CG. Pain: SG, 40 patients (80%) did not report pain 5 minutes after applying the OO. CG, 13 patients did not report pain 5 minutes after applying the drug, there were statistically significant differences. Grade and inflammation: SG, 40 patients with inflammation at 96 hours after applying the treatment, however, there were no statistically significant differences. Healing: SG, 46 patients (92%) healed at 96h. CG, 44 healed patients (88%). Response to treatment: 86% of SG was cured at 96h and 80% of CG in the same time period.
					Ozonated oil							

Leal-Rodríguez & col. ⁽¹⁹⁾ 2019	RCT	15-35	40/80	recurrent aphthous stomatitis	vitamins, diphenhydramine and mouthwash with 0.2% chlorhexidine.	healed (the clot disappears). pain, clot formed and granulation tissue formation). They were evaluated from the clinical point of view the status of the lesions and all the data referring to the time of evolution, to establish the diagnosis and establish treatment	7d	2 times a day	7d / >7d	no	Evaluation on the seventh day: SG, 93.33% cured. CG only 56.67% evolved satisfactorily. Therefore, the time required for the clinical signs of the disease to disappear was shorter when OO was applied than when conventional treatment was applied.	
Peña & col. ⁽²⁰⁾ 2019	RCT	60	>15	Not specified	chronic fibroedematous gingivitis	mouthwashes with 0.2% chlorhexidine	The status of the lesions was evaluated from the clinical point of view: healed, improved, equal or worse	6 weeks	2 times a week	6 weeks	no	In both groups, most of the patients evolved satisfactorily during the first 2 weeks of treatment. GE after the fourth visit or week of treatment, it was clinically observed the resolution of all inflammation symptoms in 70% of patients, while in CG 56.6%. In the sixth week in the EG, 96.6% of the cases were given a cure criterion, while in the CG it was 90%.
Alexandrina & col. ⁽²¹⁾ 2020	No RCT	30	Not specified	Not specified	recurrent aphthous stomatitis	Metrogil denta gel (metronidazole 10mg)	Clinical examination, including a survey, clarification of complaints, and a visual examination. For more detail, they used a bacterioscopic study.	14d	4 times a day	3 to 7 days for both groups	Not specified	Patients reported less pain on the second day of treatment, compared with traditional dental treatment. The oxygen-ozone irrigation method was less effective. Subjects in the third group, who were treated with Metrogil Denta applications,

Ozonated oil

Ozonated oil

Ozonated oil

Díaz-Couso (22) 2020	No RCT	4 6 4	> 12	215/ 249	Alveolitis, subprosthetic stomatitis, chronic fibromatous gingivitis, recurrent aphthous stomatitis, pericoronitis	Ozonated oil	Subprosthetic stomatitis (Nystatin), recurrent aphthous stomatitis (alkaline sodium perborate mouthwashes and 0.2% chlorhexidine antiseptic rinses), alveolitis (alvogyl), Pericoronitis (0.2% chlorhexidine). Chronic edematous gingivitis (0.2% chlorhexidine mouthwash)	The effectiveness of the treatment was taken into account through its favorable or unfavorable evolution to treatment during seven days, remission of symptoms and / or disappearance of the disease. For the criterion of adverse reactions, the presence of burning, redness, heat, tumor and pain in the affected area was taken into account.	7d	2 times a day	7d / >7d	no	showed the worst results. On the third day, SG had a favorable evolution of 97 patients (41.8%); Already on the seventh day there were 209 patients (90.1%). CG on the third day, only 26.2% had evolved favorably, growing to 53.3% on the fifth day. It was observed that on the seventh day there was a total absence of pain and remission of all the symptoms of oral diseases in a greater number of patients, belonging to the SG. The author considers that treatment with OO helped the patients to recover in a shorter time and almost all of them remitted the symptoms and signs presented before the first seven days. There were no adverse reactions during treatment.
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RCT: Randomized clinical trial, No RCT: Non-randomized clinical trial, N: number of participants, M: male, F: female, TF: Time of follow-up, d: Time in days, h: time in hours, AI: Application interval, SG: Study group, CG: Control group, HT: healing time, AE: Adverse effects

Table 2. Studies excluded from and reasons for their exclusion.

FIRST AUTHOR (YEAR)	TITLE OF THE PAPER	REASON FOR THE EXCLUSION
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Soler y col (2020)	Application of ozonated sunflower oil in patients affected with chronic fibroedematous gingivitis	Does not present a control group
Frías y col (2020)	Effectiveness of ozone therapy in the treatment of sub-prosthesis stomatitis in Manzanillo 2018-2019.	Does not present a control group
Céspedes y col (2019)	Usefulness of topical Oleozón® in oral ulcers in patients with mechanical artificial ventilation	There is no comparison with conventional therapy
Télles y col (2018)	Use of oleozón® in sub-prosthetic stomatitis	Does not present a control group
Jorge y col (2017)	Effectiveness of oleozón in the treatment of sub-prosthetic stomatitis in patients over 60 years of age.	Does not present a control group
Casado y col (2017)	Effectiveness of oleozon treatment versus aloe vera cream in subprosthetic stomatitis	There is no comparison with conventional therapy
Al-Omiri y col (2016)	Ozone treatment of recurrent aphthous stomatitis; a double blinded study	Does not present a control group
Kumar y col (2016)	Efficacy of Ozonated olive oil in the management of oral lesions and conditions: a clinical trial	Does not present a control group
Milanés y col (2016)	Ozone therapy in sub-prosthesis stomatitis, 2016	Does not present a control group
Armas y col (2015)	Efficacy of two natural therapies in the remission of pain in recurrent aphthous stomatitis	There is no comparison with conventional therapy
Báez y col (2015)	Ozone therapy in a patient with bucal sores	Case Report
Colás-Costa y col	The effectiveness of oleozon in the treatment of recurrent aphthous stomatitis	Does not present a control group

IV. DISCUSSION

In this SR, the effect of Ozonated oil was studied in oral lesions such as subprosthetic stomatitis, recurrent aphthous stomatitis, herpetic gingivostomatitis, pericoronitis, alveolitis and fibroedematous gingivitis. Despite the differences of the oral lesions described, there was always a positive therapeutic effect when using ozonated oil when compared with the corresponding conventional treatment. In many cases this effect was reflected as a shorter healing time or less discomfort for the patient. In the majority of the studies included, the lack of adverse effects was another point favoring Ozonated oil, showing to be a safe therapy for patients.

Relative to pericoronitis, in a SR about the standard of care for pericoronitis based on evidence, Wehr et al. (28). informed that receiving antibiotics and follow-up appointment was the most common treatment option for these cases. In spite of this, in the 3 studies included in the present SR, which were related to this event, trichloroacetic acid and 0.2% chlorhexidine mouthwashes were used and compared with the local use of the Ozonated oil, showing the latter reduced healing times with statistically significant differences (11, 12).

Alvogyl is widely used for the treatment of alveolitis. However, Alexander (29) and Bloomer (30) do not recommend it for this type of condition. Furthermore, in this SR the superiority of Ozonated oil was shown when compared with the Alvogyl with positive results in a shorter time (5). It is worth mentioning that other studies have shown some other products that produced better results than those of alvogyl. For example, Taberner et al. (31) in a SR concerning the methods used for the management of dry alveolitis, recommending laser therapy, eugenol zinc oxide and growth factor-rich plasma; whereas, Ozonated oil appears to be a simpler alternative than the growth factors-rich plasma since the Ozonated oil costs less and even allows patients to apply the product on themselves (28).

Regarding fibro edematous gingivitis, Gawron et al. (32), in their review, mentioned that the routine treatment of this type of lesion - when it is minimal and local- is based on maintaining proper oral hygiene and performing a scaling and root planing. For diffuse and advanced gingival enlargement, however, surgical intervention is necessary, with the indication of chlorhexidine mouthwashes in all cases, and the recommendation is to

investigate less invasive therapeutic methods. In the present SR, there are 2 studies (20, 22) in which the Ozonated oil, combined with a good oral hygiene, obtained favorable results and a shorter healing time when compared with the use of chlorhexidine. This could be debated considering the great antibacterial effect that has been reported for Ozonated oil in some microbiological studies (33, 34). In the cited studies, the potential of Ozonated oil to reduce the presence of periodontal pathogens and other opportunistic bacteria was shown to be equally effective than chlorhexidine (33, 34).

Subprosthetic stomatitis is regularly treated with nystatin, as its efficacy for treatment of this disease has been shown in several studies (35). Nevertheless, despite the aforementioned favorable results, 3 studies included in this SR compared the use of nystatin with ozonated oil (15, 17, 22), in which patients achieved recovery in a shorter time interval in study group (ozone oil). It is worth to mentioned that ozone oil not only has antimicrobial and anti-fungal properties, but also stimulates the immune system and promotes a site-specific wound healing (36).

Recurrent aphthous stomatitis (RAS) is the most common lesion in the oral mucosa, and although its natural history has shown that it is cured without any damage, the most severe forms need a treatment focused on reducing the pain and promoting the healing of ulcers (8,12). Corticosteroids are normally used, as well as topical application of chlorhexidine, tetracycline and diluted hydrogen peroxide (37, 38). Although there is no evidence of the bacterial origin of recurrent aphthous stomatitis, in this SR, in the 5 studies that tested treatments for this type of lesion (14, 16, 19, 21, 22), the majority compared the use of ozonated oil with local application of chlorhexidine and vitaminic supplements taken orally. The findings showed that compared with Ozonated oil, the treatments tested needed longer recovery times. These results could be associated with the antimicrobial and healing properties of the Ozonated oil (36), conferring a therapeutical advantage on it.

Herpetic gingivostomatitis is an oral lesion common in children and it is usually treated by controlling the symptoms and complemented by oral administration of Acyclovir (39, 40). In one study included in this SR, the authors used an anti-viral agent (idoxuridine) and showed a longer recovery time when compared with the Ozonated oil. In spite of the fact that there is no evidence of Ozonated oil having any antiviral properties, its known

properties of promoting and improving healing (36) allowed a quick recovery of patients, once the viral cycle of the disease had passed.

In this SR there was diversity of information and methodology of the studies included that did not allow a meta-analysis to be performed. The poor methodology was reflected in the high risk of bias. Therefore, the authors suggest that more clinical studies with higher standards of methodological rigor, need to be conducted. However, in spite of the diverse presentations in the studies selected, it was possible to observe advantages for the use of Ozonated oil in the treatment of oral lesions, achieving faster healing and the absence of adverse effects. As a result, the authors suggest that the use of ozone oil should be widely divulged throughout the dental community and scientific world, so that it may have a promising future in different types of treatment in our specialty.

V. CONCLUSION

In summary, in spite of the limited information found and the lack of methodological meticulousness of the included studies included in this SR, it was suggested that positive effects were obtained with the use of ozonated oil for the treatment of oral lesions, when compared with conventional alternatives. This effect on various types of oral lesions was found to be beneficial in terms of shorter healing times and no adverse effects, presenting a safe and reliable alternative treatment for patients suffering from soft tissue lesions.

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VERSIÓN INICIAL ENVIADA A PUBLICAR

IS THE USE OF OZONATED OIL EFFECTIVE IN THE TREATMENT OF ORAL LESIONS?
SYSTEMATIC REVIEW OF CLINICAL STUDIES

ABSTRACT: The aim of this study was to perform a systematic review (SR) of the therapeutic effect of ozonated oil on oral lesions. **Material and Methods:** A SR was conducted according to the PRISMA guidelines. The Medline (PubMed), Embase, Cochrane Library, Scielo and LILACS were searched, and hand searches, covering the period up to December 2020, were made for randomized and non-randomized clinical trials reporting the effect of ozonated oils on the management of oral lesions when compared with any other methods. The risk of bias (RoB) of the studies included were assessed by using the RoB 2 tool and ROBINS-I. **Results:** After analyzing the titles and reading the abstracts, 1932 articles were excluded; the remaining 25 passed an exhaustive full-text evaluation. Finally, 13 articles were included in this SR. There was heterogeneity of results regarding healing times and intervals of ozonated oil application for the treatment of each type of oral lesion, but in general, there was a shorter healing time when ozonated oil was used as therapy, and no adverse effects were reported. Despite the limited information found and the lack of rigorous methodological standards on the use of ozonated oil on oral lesions, a positive effect of the use of Ozonated oil for the treatment of oral lesions was suggested. **Conclusion:** The findings indicated an advantage in terms of shorter healing time when compared with other conventional treatments; furthermore, no adverse effects were reported, therefore demonstrating a safe and reliable treatment option for patients.

Key words: Mouth; Ozone; Ozoile; Therapeutics; Wounds and injuries.

RESUMEN: El objetivo de este estudio fue realizar una revisión sistemática (RS) del efecto terapéutico del aceite ozonizado sobre las lesiones orales. **Material y métodos:** Se realizó una RS siguiendo las directrices PRISMA. Se realizaron búsquedas en Medline (PubMed), Embase, Cochrane Library, Scielo y LILACS, y búsquedas manuales, que abarcaron hasta diciembre de 2020, de ensayos clínicos aleatorizados y no aleatorizados que informaran sobre el efecto de los aceites ozonizados en el tratamiento de las lesiones orales en comparación con cualquier

otro método. El riesgo de sesgo (RoB) de los estudios incluidos se evaluó mediante la herramienta RoB 2 y ROBINS-I. **Resultados:** Tras analizar los títulos y leer los resúmenes, se excluyeron 1932 artículos; los 25 restantes pasaron una evaluación exhaustiva del texto completo. Finalmente, se incluyeron 13 artículos en esta RS. Hubo heterogeneidad de resultados en cuanto a los tiempos de cicatrización y los intervalos de aplicación del aceite ozonizado para el tratamiento de cada tipo de lesión oral, pero en general, hubo un menor tiempo de cicatrización cuando se utilizó el aceite ozonizado como terapia, y no se comunicaron efectos adversos. A pesar de la limitada información encontrada y de la falta de normas metodológicas rigurosas sobre el uso de aceite ozonizado en lesiones orales, se sugirió un efecto positivo del uso de aceite ozonizado para el tratamiento de lesiones orales. **Conclusiones:** Los resultados indicaron una ventaja en términos de menor tiempo de curación en comparación con otros tratamientos convencionales; además, no se notificaron efectos adversos, por lo que se demostró una opción de tratamiento segura y fiable para los pacientes.

Palabras clave: Boca; Ozono; Terapéutica; Heridas y lesiones.

INTRODUCTION

Lesions in the oral mucosa could manifest as any change in color, appearance, swelling or loss of the integrity of the mucosal surface. Some types of these lesions may be benign and do not require any treatment, others may present acute symptoms, affecting the quality of life of the patients, causing difficulties with swallowing and speech, with symptoms of burning, irritation and pain (1). The prevalence of oral lesions in the general population worldwide can vary significantly with percentages ranging from 4.9% to 64.7% (2, 3).

The oral mucosa could be an easily accessible point of entry for infectious agents, in addition to the risk that microorganisms might have some involvement in the majority of oral lesions. Therefore, early treatment is essential to avoid future complications or the development of serious, even malignant lesions (4). There are several alternatives for conventional treatment according to the type of mucosal lesion the patient has, however, some of these have been shown to be inefficient, by generating discomfort to the patients and requiring relatively extended treatment times. In view of the foregoing, there are treatment alternatives in natural and traditional medicine that are used as therapy in oral diseases, such as ozone therapy that has shown good results due to its properties (5).

Ozone is a natural gaseous molecule formed by 3 oxygen atoms. Included among its unique features are the properties of being immunostimulant, analgesic, anti-hypnotic, detoxifying, antimicrobial, and being capable of performing bioenergetic and biosynthetic actions. Due to its atraumatic, painless, non-invasive characteristics, it does not cause discomfort or secondary effects, thus it is highly reliable and patients readily accept treatment with it (6). There are 3 ways to apply the ozone: ozone gas; it can be applied directly, as ozonated water or as ozonated oil (7).

Ozonated oil results from the reaction of ozone with fatty acids and other substances, and procedure of ozonation is achieved by means of bubbling ozone through of a generator. During this reaction, substances such as peroxides, ozone, aldehydes, ketones, among others, are formed (8, 9). Ozonated oil that comes into contact with exudates or injuries is split and generates ozone, which breaks down releasing hydrogen peroxide and lipoperoxides, which would be responsible for the regenerative and disinfectant effects. This slow release of ozone further promotes the healing process by acting as a local antimicrobial agent and promoting cytokine release with an effect on tissue repair (10).

There are many studies in which ozonated oil has been used as an agent for the treatment of different types of oral lesions, showing better results when compared with their respective conventional treatments, such as less time taken for healing to occur, greater comfort for patients and absence adverse effects (5, 11-22), however, there is no consensus about its use, benefits or the ideal treatment time. Therefore, a systematic review was conducted to answer the following focused question based on PICO strategy:

Is the use of ozonated oil effective in the treatment of ulcerated lesions of the oral mucosa? and Is the use of ozonated oil effective in the treatment of oral bone lesions?

MATERIAL AND METHODS

Protocol and registration

This SR was conducted in accordance with the Transparent Reporting of Systematic Reviews and Meta-Analysis – PRISMA Statement (23) and was registered at PROSPERO with number CRD42021237068.

Focused question

The focused questions to be addressed were:

1. Is the use of ozonated oil effective in the treatment of ulcerated lesions of the oral mucosa?
2. Is the use of ozonated oil effective in the treatment of oral bone lesions?

Eligibility Criteria

The inclusion criteria for this SR were the following: Clinical studies that use ozonated oil as a treatment for different forms of oral lesions (subprosthetic stomatitis, recurrent aphthous stomatitis, and herpetic gingivostomatitis, and pericoronaritis, alveolitis and fibroedematous gingivitis). Literature reviews, letters to the editor, short communications, case reports, pilot studies and trials that analyze other applications of Ozonated acceptance not related to oral injuries are excluded.

Search strategy

The MEDLINE (PubMed), Embase, Cochrane Library, Scielo and LILACS databases were searched up to March 2021 by two independent reviewers (J.Y and J.A). The search was performed without restrictions on dates or language. The search strategy was applied as follows: PubMed: ("Aphthous stomatitis" OR "Dry Socket" OR "Pericoronitis" OR "Herpetic

Stomatitis" OR "subprosthetic stomatitis" OR "fibroedematous" OR "alveolitis" OR osteomyelitis OR "Aphthous Ulcer" OR "Aphthous Stomatitides" OR "Alveolar Osteitis" OR "Herpetic Gingivostomatitis" OR "Oral Herpes Simplex" OR "oral injury" OR "oral lesion") AND ("ozonated oil" OR "Ozonated" OR "ozonation" OR "ozone" OR "Ozonized" OR "ozone therapy" OR "ozonotherapy" OR "ozonating" OR "oleozon" OR "vegetable oils" OR "plant oils" OR "ozonation"). In addition, the grey literature in the System for Information on Grey Literature in Europe (<http://www.opengrey.eu>) and Google Scholar databases were screened electronically, as recommended by the high standards for systematic reviews (AMSTAR guideline) (24). Finally, the list of references of studies included were also hand searched to capture any potential additional records, as suggested by Greenhalgh and Peacock (25).

Data collection, extraction and management

Screening and selection of articles?

Titles and abstracts were screened by two reviewers independently (JY. and JA). Full-text reports were obtained and reviewed independently for studies that appeared to meet the previously mentioned inclusion criteria. Kappa scores (Cohen's κ coefficient) were used during full-text assessment to ensure eligibility and level of agreement between the reviewers. Disagreements were resolved by discussion and consulting a third reviewer (GM).

Data extraction

The studies that fulfilled the eligibility criteria were processed for data extraction, conducted by two independent researchers, using predefined spreadsheets. Disagreements were resolved by discussion with a third reviewer. In the event of missing data, a request was sent to the authors by e-mail. For each study selected, the following variables were collected: 1) characteristics of the study: author, year of publication, country, design of the study (randomized clinical trial and non-randomized); 2) demographic data: size of sample, average age (years) and sex (male / female); 3) outcome measures: healing time, application interval and adverse effects (presence or absence).

Risk of bias in individual studies

Two reviewers (J.M.M and J.Y) evaluated the risk of bias in studies selected, using the Cochrane tool for risk of bias assessment, RoB 2 (version 2, available at: <https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2>).

The authors of this SR decided to evaluate the result related to "assignment to the

intervention (the effect for the purpose of treating)" and five domains were examined: bias that arises from the assignment to randomization and the process of concealing the treatments, bias due to deviations from the planned interventions that affected the involvement of the participants and a team of researchers, although there were missing result data, the result measurement and the result selection were selected. Based on the responses to the questions and the algorithms of the tool, it was considered that each domain had "low risk of bias", "some concerns related to risk of bias" or "high risk of bias". The studies were categorized as low risk of bias (all domains had low risk of bias), high risk of bias (one or more domains had high risk of bias) and concerning (when one or more domains had some concerns) (26). The decisions were resolved by means of discussion, consulting a third advisor (G.M).

The non-randomized controlled trials were evaluated by means of the ROBINS-I tool. (27) Each controlled trial was classified as low information, or as low, moderate, severe and critical risk of bias. The discrepancies between the reviewers were resolved by means of open discussion. In the event that an agreement could not be achieved, the final decision was made by another co-author (G.M).

The following domains have evolved to not randomized controlled trials (27):

- Preintervention
 - Bias due to confusion
 - Bias in the selection of participants in the study
- In intervention
 - Bias in the classification of interventions
- Post-intervention
 - Bias due to deviations from planned interventions
 - Bias due to missing data
 - Bias in the results measurement
 - Bias in the selection of the informed result

To demonstrate the general risk of bias, each study included was classified as low, moderate, severe and critical risk of bias or the absence of information according to the following criteria:

- Low risk of bias: the study is considered to have a low risk of bias for all domains.
- Moderate risk of bias: the study is considered to have a low to moderate risk of bias for all domains.

- Severe risk of bias: the study is considered to have a severe risk of bias for at least one domain, but it does not have a critical risk of bias for any domain.
- Critical risk of bias: the study is considered to have a critical risk of bias in at least one domain.
- No information: there is no clear indication that the study has a serious or critical risk of bias and there is a lack of information on the most key domains for bias (a judgment is required for this).

RESULTS

Study Selection

The electronic search strategy identified 1957 articles. After analyzing the titles and abstracts, 1932 studies were excluded, the remaining 25 were subject of an exhaustive evaluation of the full text, from which 12 were excluded not fulfilling the eligibility criteria. As a result, 13 papers were included in this SR (Figure 1).

Study characteristics

The thirteen randomized (5, 11, 12, 14, 16, 18-20) and non-randomized clinical trials (13, 15, 17, 21, 22) included were conducted between 2010 and 2020, and their main methodological characteristics are presented in Table 1. All clinical studies showed the effective outcome of the Ozonated oil on different types of oral lesions: subprosthetic stomatitis, recurrent aphthous stomatitis, herpetic gingivostomatitis, pericoronitis, alveolitis and fibro edematous gingivitis; and used as a control and conventional treatment for each type of oral lesion. A total of 1644 patients from different age groups were included in the present SR. Participants in 3 studies suffering from pericoronitis (11, 12, 22), participants in 3 studies developing alveolitis (5, 18, 22), 5 studies developed in patients with recurrent aphthous stomatitis (14, 16, 19, 21, 22), 3 studies based on subprosthetic stomatitis (15, 17, 22), another 2 studies were based on patients with fibroedematous gingivitis (20, 22), lastly a only study contemplating the use of Ozonated oil for patients with herpes related gingivostomatitis (13). In all studies the local application of Ozonated oil was used as therapy. The follow-up periods varied from 72 hours to 6 weeks, depending on the type of wound.

Ozonated oil in pericoronitis

In 2 RCTs (11, 12) and 1 non RCT(22) authors reported the use of the ozonated oil as therapy for pericoronitis and compared it with conventional therapy consisting of 50% trichloroacetic acid and mouthwashes with 0.2% chlorhexidine for a period of time between 3

to 7 days, an interval of application of between 3 to 4 times a day, with a healing time between 72 hours and 7 days, a larger number of patients recovered in less time in the study group (ozonated oil), while the control groups showed lower numbers of patients satisfied in the same period of time, showing statistically significant differences. No adverse effects were reported.

Ozonated oil in alveolitis

In 2 RCT (5, 18) and 1 non RCT (22) Ozonated oil treatment was used as a treatment for alveolitis and compared it with alvogyl. All the studies had a 7-day follow-up period, the time interval in which the healing took place. The lesions healing times were heterogeneous, varying between 4 days (18), 5 days (5) or up to 7 days (22) for study group (ozonated oil), the interval of application varied from 4 times a day (22) up to every 72 hours (5), no adverse effects were reported. In all cases, a shorter recovery time was observed when Ozonated oil was used as therapy. However, only one study (5) reported statistically significant differences.

Ozonated oil in fibroedematous gingivitis

Only 2 studies: 1 RCT (20) and 1 non RCT (22), used the Ozonated oil therapy for fibroedematous gingivitis and it was compared with the use of chlorhexidine mouthwashes at 0.2%, the healing time varied between 7 days (22) showing only favorable results in study group (ozonated oil) and 6 weeks (20) (in which 96.6% of patients were cured in the study group), the interval of application varied from 2 times a week (20) to 4 times a day (22), no adverse effects were reported. In both studies there was a shorter healing time when Ozonated oil was used as therapy.

Ozonated oil in subprosthetic stomatitis

Three (15, 17, 22) of the studies included in this SR (non RCT) used ozonated oil as treatment for subprosthetic stomatitis and compared it with conventional treatment consisting of nystatin. The follow-up time ranged from 7 days (17, 22) to 15 days (15), on the other hand, the interval of application of ozonated oil for this type of injury varied from once a day (15, 17) to 2 times a day (22). The healing time found in the studies varied from 7 days (17, 22) up to 12 days (15). In all the studies, there was a shorter recovery time when Ozonated oil was used as therapy compared with treatment with nystatin. No adverse effects were reported.

Ozonated oil in recurrent aphthous stomatitis

In 3 RCTs (14, 16, 19) and 2 non RCT (21, 22) studies the Ozonated oil was used to treat recurrent aphthous stomatitis and compared it with other therapies such as: multivitamins and

0.2% chlorhexidine mouthwashes (14, 19), sodium perborate alkaline mouthwashes and 0.2% chlorhexidine mouthwashes (16, 22), and finally a comparative study with metronidazole gel (21), with a follow-up time ranging from 7 (14, 16, 19, 22) to 14 days (21), an interval of application of between 2 (14, 19, 22) to 4 (16, 21) times a day, as a healing time between 5 (14) and 7 days (16, 19, 21, 22). In all cases, a shorter recovery time was observed when Ozonated oil was implemented as therapy. Only 2 studies (19, 21) reported statistically significant differences. No adverse effects were reported.

Ozonated oil in herpetic gingivostomatitis

Only 1 non RCT study (13) included in the present SR implemented the Ozonated oil as therapy for herpetic gingivostomatitis and compared it with the use of idoxuridine at 0.1% with a follow-up period of 10 days, the healing time was ≤ 8 days for the control group, the interval of application was once a day, without specifying the presence of the adverse effects. The patients treated with the Ozonated oil had a shorter healing time of the lesion.

Risk of bias in the studies selected

In RCT studies, inadequate methods of generating sequences and assigning participants were found in all of the publications (90%) included and only one study showed a correct assignment process between groups (Figure 2). Among the deviations from the planned interventions, 60% of the studies were classified as "high" due to problems with the masking process (Figure 3). However, it was not possible to mask the entire staff due to the experimental context. Finally, all studies reported results without a pre-specified plan. In general, it was considered that only one study had a clear risk of bias. Figures 2 and 3 show a summary of the results.

Three of the non RCT studies were classified as having a severe risk of bias (15-17), one study with a moderate risk of bias (21) and one study was classified as having a critical risk of bias (13) as shown in Figure 4.

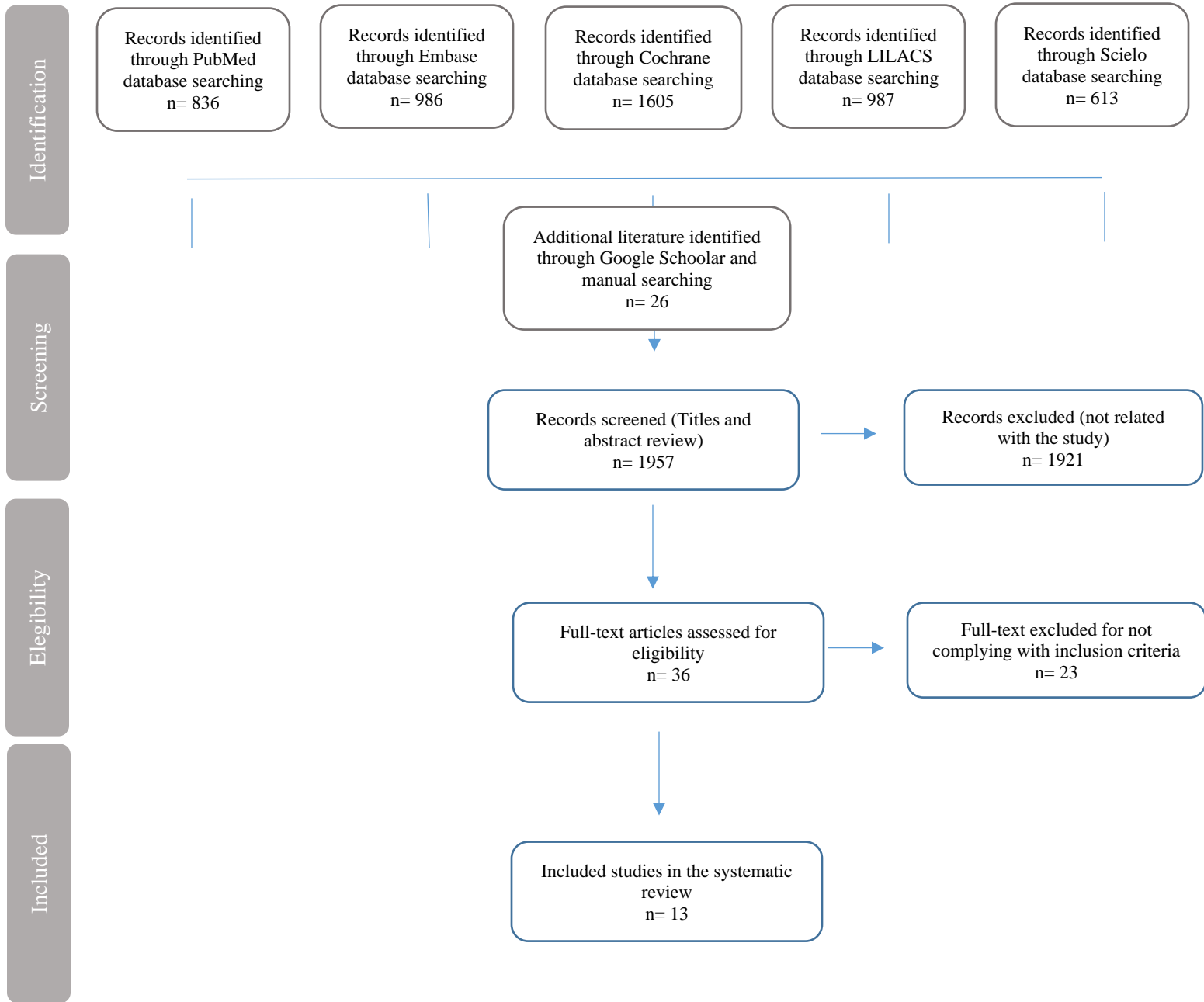


Figura 1. Flow chart of manuscripts selected through the review process.



Figure 2. Risk of bias summary of the clinical trials, included in the systematic review, based on the Cochrane risk of bias tool, RoB 2.

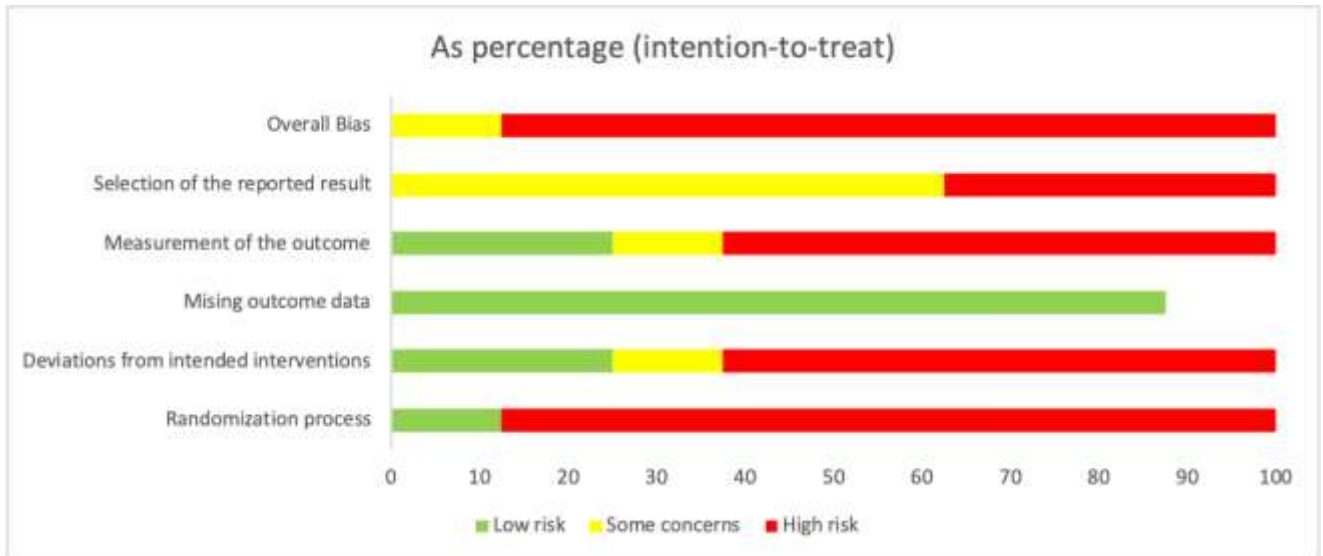


Figure 3. Risk of bias summary as a percentage of the clinical trials included in the systematic review.

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Alexandrina et al; 2020	+	?	-	+	+	+	+	-
Diaz et al; 2020	+	+	-	+	+	X	+	X
Jimenez et al; 2018	+	+	X	+	+	X	+	X
Castillo et al; 2018	+	+	-	X	+	X	+	X
Rodriguez et al; 2012	+	+	-	-	+	!	+	!

Domains:

D1: Bias due to confounding.
 D2: Bias due to selection of participants.
 D3: Bias in classification of interventions.
 D4: Bias due to deviations from intended interventions.
 D5: Bias due to missing data.
 D6: Bias in measurement of outcomes.
 D7: Bias in selection of the reported result.

Judgement

! Critical
 X Serious
 - Moderate
 + Low
 ? No information

Figure 4. Risk of bias summary of the non-randomized clinical trials included in the systematic review, based on the tool ROBINS-I.

Table 1. Main characteristics of the included studies in the systematic review

Author and year	Design	N	Age	Gender (M/F)	Type of oral lesion	Test group	Control group (CG)	Assessed parameters	TF	AI	HT SG/CG	AE	Results
Mayor & col. ⁽¹¹⁾ 2010	RCT	90	> 15	25/65	pericoronitis	Ozonated oil	50% trichloroacetic acid	Clinical evaluation: satisfactory (improvement or cure at 72h), unsatisfactory (equal to or worse at 72h). Efficacy of the study drug: good (satisfactory clinical evolution), poor (unsatisfactory clinical evolution)	72h	3 times a day	72h/>72h	no	100% good efficacy for SG (OO), 62% good efficacy and 38% poor efficacy for CG (trichloroacetic acid).
Mayor & col. ⁽¹²⁾ 2011	RCT	90	> 15	Not specified	pericoronitis	Ozonated oil	50% trichloroacetic acid	Microbiological evaluation: satisfactory (field absent or scarce, Gram- not predominant), unsatisfactory (abundant field or covered field, Gram- predominate). Degree of patient satisfaction (satisfied vs not satisfied, according to the patient's appreciation) and adverse effects (yes or no)	72h	3 times a day	72h/>72h	no	Microbiological evaluation, satisfactory SG in 43 patients (96%), satisfactory CG in 18 patients (40%). Patient's satisfaction: Satisfactory SG 43 patients (96%), CG 30 patients (66%).
Rodriguez & col. ⁽¹³⁾ 2012	No RCT	250	<9	82/168	Herpetic gingivostomatitis	Ozonated oil	0.1% idoxuridine	Evolution: Cured: When there are no clinical signs of Acute Herpetic Gingivostomatitis. Not cured: When there are clinical signs of Acute Herpetic Gingivostomatitis in the oral cavity	10d	1 time a day	≤8d/8a/10d	no	79 patients treated with OO (63.2%) cured in < 6 days, 78 patients treated with idoxuridine (62.4%) were cured in 9 to 10 days; the treatment with OO minimized the healing time.
Martinez-Abreu & col. ⁽⁵⁾ 2015	RCT	100	20-59	56/44	Alveolitis	Ozonated oil	Alvogyl	Clinical: recovered (pain and inflammation disappear), improved (pain and inflammation decrease), the same (pain maintains intensity and inflammation persists), worse (pain and	7d	Every 72h	3 to 4 days/>3,4 days	Not specified	100 patients in 2 groups: 50 SG (OO) and 50 CG (alvogyl) The patients were evaluated at 72h (2nd visit), 96h (3rd visit) and at one week of treatment (4th visit). 41 SG patients only

Fontaine & col. ⁽¹⁴⁾ 2016	RCT	8 0	> 12	26/5 4	recurrent aphthous stomatitis	vitamins and mouthwash with 0.2% chlorhexidine.	inflammation persists or worsens). Microbiological: infected (presence of mopyogens), free of infection (absence of mopyogens Efficacy evaluation: good (clinical criterion of recovered and microbiological free of infection), acceptable (clinical criterion of improved and microbiological free of infection) and poor (clinical criterion of equal or worse and microbiological infected). Clinical evaluation: satisfactory (the pain decreases or disappears; the size of the lesion decreases or disappears) not satisfactory (the pain persists and there is no change in the lesion). Healing: cured (there are no clinical signs of stomatitis) and not cured (there are clinical signs of stomatitis in the mucosa). Degree of satisfaction: satisfied and not satisfied (for both criteria the perception of the patients was taken into account).	7d	2 times a day	4 to 5 days / >7 days	no	needed 2 visits to recover, CG only 29 patients. For the microbiological evaluation: From 20 patients in the SG 13 patients showed signs of recovery from infection, while in the CG from the 20 evaluated patients only 6 showed the same result. SG and CG 40 patients each. OS: 34 patients needed only two to three applications to consider a satisfactory clinical evaluation, 38 patients only needed a maximum of 4 to 5 days to consider themselves cured. CG: 18 patients needed more than 7 days. Degree of satisfaction: 97.5% of the GE satisfied.
						Ozonated oil						
Castillo & col. ⁽¹⁵⁾ 2018	No RCT	6 8	>19	17/5 1	subprosthetic stomatitis	nystatin	Clinical evaluation, healing was determined as the lesion disappeared and the physiological mucosa became	15d	1 time a day	4 to 12d / 7 to 15d	no	CG the mucosa recovered normality between 10 to 12 days (52.9% of the sample). Only 14.7% achieved it between 7 and 9 days; no patient was healed during the first week of treatment.
						Ozonated oil						

Diaz-Couso & col. ⁽¹⁶⁾ 2018	RCT	3 2	> 12	12/2 0.	recurrent aphthous stomatitis	Ozonated oil	alkaline mouthwashes sodium perborate and mouthwashes 0.2% chlorhexidine	Cured , there is a good general condition of the affected area (remission of symptoms) and disappearance of the ulcer. Not cured , permanence of the ulcer, the symptoms do not subside with the application of the medicine. For the criterion of adverse reactions, the presence in the affected area of burning, redness, heat, tumor and pain was taken into account.	7d	4 times a day	3 to 7 days on both groups	no	SG 44.1% of patients reached normality of the mucosa between 7 to 9 days, 32.4% reached normality between 4 to 6 days. 76.6% of the SG patients healed before 10 days of application. On the third day, the eight SG patients evolved favorably (50%) and in the CG it was 12.5%. In general the evolution of the treatment, cured patients: SG 93.7% and CG 68.7%.
Jimenez & col. ⁽¹⁷⁾ 2018	No RCT	4 0	> 20	17/2 3	subprosthetic stomatitis	Ozonated oil	nystatin	Treatment effectiveness: Very effective, effective and not very effective.	7d	1 time a day	4 to days/ >7 days	no	Evaluation of the effectiveness of treatment in sub-prosthesis stomatitis: SG, effective treatment in 14 patients (35.0%), CG, ineffective treatment with 18 patients (45.0%). The daily application of OO was effective for the treatment of this disease between four and seven visits to consultation, healing time was shorter compared to nystatin cream in the CG.
Souto & col. ⁽¹⁸⁾ 2018	RCT	1 0 0	20- 59	Not specified	alveolitis		alvogyl	Pain (referred by the patient at the beginning and after the application of	7d	1 applicati on	4 to 5d/ >7 d	Not specif ied	Pain: SG, 40 patients (80%) did not report pain 5 minutes after

Ozonated oil

the treatments at 5, 15, and 30 minutes, visual analog scale)

Inflammation

(state of the mucosa surrounding the alveolus, by direct observation: inflamed (hyper-colored, increased in volume, smooth); slightly inflamed (slightly hyper-colored and slight increase in volume) and non-inflamed (normally colored, resilient and normal size).

Scarring: non-healing (delayed clot formation, stench, hypersensitivity in the walls of the alveolus), partial scarring (despite the new clot formation, presents hypersensitivity, slight stench) and total scarring (alveolus occupied by a new blood clot), with formation of granulation tissue and proliferation of the epithelium on the external surface).

Response to treatment: no response to treatment (same patient, pain does not disappear, no clot formation, hypersensitive alveolus walls and stench), improved (not intense pain, slight stench and new clot formation) and healed (the clot disappears). pain, clot formed and granulation tissue formation).

applying the OO. CG, 13 patients did not report pain 5 minutes after applying the drug, there were statistically significant differences.

Grade and inflammation: SG, 40 patients with inflammation at 96 hours after applying the treatment, however, there were no statistically significant differences.

Healing: SG, 46 patients (92%) healed at 96h. CG, 44 healed patients (88%).

Response to treatment: 86% of SG was cured at 96h and 80% of CG in the same time period.

Leal-Rodríguez & col. (19) 2019	RCT	15-35	40/80	recurrent aphthous stomatitis	vitamins, diphenhydramine and mouthwash with 0.2% chlorhexidine.	Ozonated oil	They were evaluated from the clinical point of view the status of the lesions and all the data referring to the time of evolution, to establish the diagnosis and establish treatment	7d	2 times a day	7d / >7d	no	Evaluation on the seventh day: SG, 93.33% cured. CG only 56.67% evolved satisfactorily. Therefore, the time required for the clinical signs of the disease to disappear was shorter when OO was applied than when conventional treatment was applied.	
Peña & col. (20) 2019	RCT	60	>15	Not specified	chronic fibroedematous gingivitis	Ozonated oil	mouthwashes with 0.2% chlorhexidine	The status of the lesions was evaluated from the clinical point of view: healed, improved, equal or worse	6 weeks	2 times a week	6 weeks	no	In both groups, most of the patients evolved satisfactorily during the first 2 weeks of treatment. GE after the fourth visit or week of treatment, it was clinically observed the resolution of all inflammation symptoms in 70% of patients, while in CG 56.6%. In the sixth week in the EG, 96.6% of the cases were given a cure criterion, while in the CG it was 90%.
Alexandrina & col. (21) 2020	No RCT	30	Not specified	Not specified	recurrent aphthous stomatitis	Ozonated oil	Metrogildenta gel (metronidazole 10mg)	Clinical examination, including a survey, clarification of complaints, and a visual examination. For more detail, they used a bacterioscopic study.	14d	4 times a day	3 to 7 days for both groups	Not specified	Patients reported less pain on the second day of treatment, compared with traditional dental treatment. The oxygen-ozone irrigation method was less effective. Subjects in the third group, who were treated with Metrogil Denta applications, showed the worst results.
Díaz-Couso (22) 2020	No RCT	46	>12	215/249	Alveolitis, subprosthetic stomatitis, chronic fibromatous	Ozonated oil	Subprosthetic stomatitis (Nystatin), recurrent	The effectiveness of the treatment was taken into account through its favorable or unfavorable	7d	2 times a day	7d / >7d	no	On the third day, SG had a favorable evolution of 97 patients (41.8%); Already on the

s gingivitis, recurrent aphthous stomatitis, pericoronitis	Ozonated oil	aphthous stomatitis (alkaline sodium perborate mouthwashes and 0.2% chlorhexidine antiseptic rinses), alveolitis (alvogyl), Pericoronitis (0.2% chlorhexidine). Chronic edematous gingivitis (0.2% chlorhexidine mouthwash)	evolution to treatment during seven days, remission of symptoms and / or disappearance of the disease. For the criterion of adverse reactions, the presence of burning, redness, heat, tumor and pain in the affected area was taken into account.	seventh day there were 209 patients (90.1%). CG on the third day, only 26.2% had evolved favorably, growing to 53.3% on the fifth day. It was observed that on the seventh day there was a total absence of pain and remission of all the symptoms of oral diseases in a greater number of patients, belonging to the SG. The author considers that treatment with OO helped the patients to recover in a shorter time and almost all of them remitted the symptoms and signs presented before the first seven days. There were no adverse reactions during treatment.
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RCT: Randomized clinical trial, No RCT: Non-randomized clinical trial, N: number of participants, M: male, F: female, TF: Time of follow-up, d: Time in days, h: time in hours, AI: Application interval, SG: Study group, CG: Control group, HT: healing time, AE: Adverse effects

Table 2. Studies excluded from and reasons for their exclusion.

FIRST AUTHOR (YEAR)	TITLE OF THE PAPER	REASON FOR THE EXCLUSION
Soler y col (2020)	Application of ozonated sunflower oil in patients affected with chronic fibroedematous gingivitis	Does not present a control group
Frías y col (2020)	Effectiveness of ozone therapy in the treatment of sub-prosthesis stomatitis in Manzanillo 2018-2019.	Does not present a control group
Céspedes y col (2019)	Usefulness of topical Oleozón® in oral ulcers in patients with mechanical artificial ventilation	There is no comparison with conventional therapy
Télles y col (2018)	Use of oleozón® in sub-prosthetic stomatitis	Does not present a control group
Jorge y col (2017)	Effectiveness of oleozón in the treatment of sub-prosthetic stomatitis in patients over 60 years of age.	Does not present a control group
Casado y col (2017)	Effectiveness of oleozon treatment versus aloe vera cream in subprosthetic stomatitis	There is no comparison with conventional therapy
Al-Omiri y col (2016)	Ozone treatment of recurrent aphthous stomatitis; a double blinded study	Does not present a control group
Kumar y col (2016)	Efficacy of Ozonated olive oil in the management of oral lesions and conditions: a clinical trial	Does not present a control group
Milanés y col (2016)	Ozone therapy in sub-prosthesis stomatitis, 2016	Does not present a control group
Armas y col (2015)	Efficacy of two natural therapies in the remission of pain in recurrent aphthous stomatitis	There is no comparison with conventional therapy
Báez y col (2015)	Ozone therapy in a patient with bucal sores	Case Report
Colás-Costa y col	The effectiveness of oleozon in the treatment of recurrent aphthous stomatitis	Does not present a control group

DISCUSSION

In this SR, the effect of Ozonated oil was studied in oral lesions such as subprosthetic stomatitis, recurrent aphthous stomatitis, herpetic gingivostomatitis, pericoronitis, alveolitis and fibroedematous gingivitis. Despite the differences present in each type of oral lesion, there was always a positive therapeutic effect with respect to the use of ozonated oil when compared with the corresponding conventional treatment. In many cases this effect was reflected as a reduced healing time or greater comfort for the patient. In the majority of the studies included, the lack of adverse

effects was another point in favor of the Ozonated oil treatment, as it was shown to be a safe therapy for patients.

Relative to pericoronitis, in a SR about the standard of care for pericoronitis based on evidence, Wehr et al (28) informed that receiving antibiotics and scheduling a follow-up appointment was the most common treatment option for these cases. In spite of this, in the 3 studies included in the present SR, which were related to this event, trichloroacetic acid and 0.2% chlorhexidine mouthwashes were used and compared with the local use of the Ozonated oil, showing the latter reduced healing times with statistically significant differences (11, 12).

Alvogyl is widely used for the treatment of alveolitis. However, Alexander (29) and Bloomer (30) do not recommend it for this type of condition. Furthermore, in this SR the superiority of Ozonated oil was shown when compared with the Alvogyl with positive results in a shorter time (5). It is worth mentioning that other studies have shown some other products that produced better results than those of alvogyl. For example, Taberner et al (31) in a SR concerning the methods used for the management of dry alveolitis, recommending laser therapy, eugenol zinc oxide and growth factor-rich plasma; whereas, Ozonated oil appears to be a simpler alternative than the growth factors-rich plasma since the Ozonated oil costs less and even allows patients to apply the product on themselves (28).

Regarding fibro edematous gingivitis, Gawron et al (32), in their review, mentioned that the routine treatment of this type of lesion - when it is minimal and local- is based on maintaining proper oral hygiene and performing a scaling and root planing. For diffuse and advanced gingival enlargement, however, surgical intervention is necessary, with the indication of chlorhexidine mouthwashes in all cases, and the recommendation is to investigate less invasive therapeutic methods. In the present SR, there are 2 studies (20, 22) in which the Ozonated oil, combined with a good oral hygiene, obtained favorable results and a shorter healing time when compared with the use of chlorhexidine. This could be debated considering the great antibacterial effect that has been reported for Ozonated oil in some microbiological studies (33, 34). In the cited studies, the potential of Ozonated oil to reduce the presence of periodontal pathogens and other opportunistic bacteria was shown to be equally effective than that of chlorhexidine (33, 34).

Subprosthetic stomatitis is regularly treated with nystatin, as its efficacy for treatment of this disease has been shown in several studies (35). Nevertheless, despite the afore-mentioned good

results, 3 studies included in this SR compared the use of nystatin with ozonated oil (15, 17, 22), in which patients achieved recovery in a shorter time interval in study group (ozone oil). It must be remembered that ozone oil not only has antimicrobial and anti-fungal properties, but also stimulates the immune system and promotes wound healing at the site of the lesion (36).

Recurrent aphthous stomatitis (RAS) is the most common lesion in the oral mucosa, and although its natural history has shown that it is cured without any damage, the most severe forms need a treatment focused on reducing the pain and promoting the healing of ulcers (8,12). Corticosteroids are normally used, as well as topical application of chlorhexidine, tetracycline and diluted hydrogen peroxide (37, 38). Although there is no evidence of the bacterial origin of recurrent aphthous stomatitis, in this SR, in the 5 studies that tested treatments for this type of lesion (14, 16, 19, 21, 22), the majority compared the use of ozonated oil with local application of chlorhexidine and vitamin supplements taken orally. The findings showed that compared with Ozonated oil, the treatments tested needed longer recovery times. These results could be associated with the antimicrobial and healing properties of the Ozonated oil (36), conferring a therapeutical advantage on it.

Herpetic gingivostomatitis is an oral lesion common in children and it is usually treated by controlling the symptoms and complemented by oral administration of Acyclovir (39, 40). In one study included in this SR, the authors used an anti-viral agent (idoxuridine) and showed a longer recovery time when compared with the Ozonated oil. In spite of the fact that there is no evidence of Ozonated oil having any antiviral properties, its known properties of promoting and improving healing (36) allowed a quick recovery of patients, once the viral cycle of the disease had passed.

In this SR there was diversity of information and methodology of the studies included that did not allow a metanalysis to be performed. The poor methodology was reflected in the high risk of bias. Therefore, the authors suggest that a larger number of clinical studies with higher standards of methodological rigor, need to be conducted. However, in spite of the diverse presentations in the studies selected, in general it was possible to observe a slight advantage of the use of Ozonated oil in the treatment of oral lesions, achieving faster healing and the absence of adverse effects. As a result, the authors suggest that the use of ozone oil should be widely divulged throughout the dental community and scientific world, so that it may have a promising future in different types of treatment in our specialty.

CONCLUSION

In summary, in spite of the limited information found and the lack of methodological meticulousness of the studies included in this SR, the results suggested that positive effects were obtained with the use of ozonated oil for the treatment of oral lesions, when compared with conventional alternatives. This effect on various types of oral lesions was found to be beneficial in terms of shorter healing times and no adverse effects were reported, therefore, presenting a safe and reliable alternative treatment for patients suffering from soft tissue lesions.

COPIA DE CARTAS DE RESPUESTA A LAS OBSERVACIONES DE LOS REVISORES

De: PhD Jessie Reyes-Carmona via Journals of University of Costa Rica <jreves@ucr.ac.cr>

Enviado: lunes, 11 de septiembre de 2023 11:29

Para: Yuri Castro Rodríguez <yuricastro_16@hotmail.com>

Asunto: [JDS] Editor Decision

Yuri Castro Rodríguez,

We have reached a decision regarding your submission to *Odonatol - International Journal of Dental Sciences*, "Is the use of ozonated oil effective in the treatment of oral lesions? Systematic review of clinical studies".

Our decision is: **Revisions Required**. Please perform all suggestions asked by the reviewers. Moreover there is a huge amount of grammar mistakes, send the manuscript to a professional editing service. After that please send the final manuscript to jessie.reves@ucr.ac.cr.

Reviewer A:

Recommendation: See Comments

Information contained

Original but moderately interesting

Title:

- Adequately informative

Suggestions to Title/Structure of the manuscript

- The manuscript is Clear and concise

Comments regarding the structure of the manuscript, abstract, keywords:

Introducción

- La cita va antes del signo de puntuación (punto, coma, etc.).
- En el tercer párrafo de la introducción colocar la "O" en minúscula: "... as Ozonated water or as ozonated oil"

Palabras clave Ozonol verificar que sea "MeSH Headings"

Materials and Methods

- Are sufficient details of the methods been included?
- Are the methods appropriate?

Suggestions to materials and methods:Results:

- Are the results presented in an appropriate manner?
- Is the statistical evaluation adequate?

Tables and illustrations:

- Is the use of tables and illustrations appropriate?
- Are the captions/legends appropriate?

Suggestions to the results section, tables and illustrations :

La Tabla 1 orientaría de manera horizontal.

Discussion and Conclusions:

- Is the method discussed?
- Are the results discussed?
- Are the conclusions clear and justified?

References:

- Is the relevant literature quoted?

Suggestions Discussion, Conclusions and References

Discusión:

- Agregar la referencia bibliográfica correspondiente a las oraciones que les falta, hay párrafos de varias oraciones con solo una referencia

Bibliografía:

- Verificar que toda la bibliografía esté en formato Vancouver y agregar el doi de cada una.

Overall scientific priority:

Moderate

Comments to Author:

El artículo es publicable realizando los cambios sugeridos.

Reviewer Recommendation Term:

Article accepted with minor changes

ODOVTOS-International Journal of Dental Sciences REVISTA



KATTIA CAMPOS CHAVES KATTIA.CAMPOS@uncc.ac.cr
(para publicación, R. M. Alvarado)

100 100 4 100 100 100

Buenos días doctores. Adjunto arte del artículo "Is the Use of Ozonated Oil Effective in the Treatment of Oral Lesions? Systematic Review of Clinical Studies" para su revisión y aprobación.

Información pendiente:

1. Título del artículo en español.
2. Grados académicos de todos los autores (en siglas).
3. Correo electrónico de todos los autores.
4. Declaración de contribución del autor, según: <https://revistas.uncc.ac.cr/index.php/ODOVTOS/about/submissions>
5. Completar las siguientes referencias: 5, 10, 11, 13, 14, 15, 16, 21, 22, 28, 32, 39

Quedo a la espera para continuar con el proceso de publicación.



FOD

Facultad de Odontología

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VERSIÓN EN ESPAÑOL

I. INTRODUCCIÓN

Una lesión de la mucosa oral se puede presentar como cualquier modificación en el color, aspecto de la superficie, hinchazón o pérdida de la integridad de la superficie de la mucosa. Aunque muchas de ellas son benignas y no requieren tratamiento, algunas pueden presentar sintomatología aguda, afectando la calidad de vida de los pacientes, teniendo consecuencias en la masticación, deglución y el habla, con síntomas de ardor, irritación y dolor.(1) La prevalencia de lesiones orales en la población a nivel mundial puede variar significativamente con porcentajes que van desde el 4.9% al 64.7%.(2-3)

La mucosa oral puede ser un lugar de fácil acceso para la introducción de agentes infecciosos, en adición a esto, hay que tener en cuenta que en la mayoría de lesiones orales están implicados microorganismos, por lo cual el tratamiento precoz de las mismas resulta fundamental para evitar complicaciones futuras o el desarrollo de lesiones más serias, incluso malignas.(4) Existen diversas alternativas de tratamiento convencional según el tipo de lesión de la mucosa que presente el paciente, sin embargo, son todavía tratamientos ineficientes, con mucho discomfort por parte de los pacientes y tiempos de tratamiento relativamente largos. Frente a esto, en la medicina natural y tradicional existen alternativas de tratamiento que se están utilizando como terapéutica en enfermedades bucales, la ozonoterapia es una de ellas, demostrando buenos resultados debido a sus propiedades.(5)

El ozono es una molécula gaseosa natural formada por 3 átomos de oxígeno. Sus propiedades son únicas e incluyen acciones inmunoestimulantes, analgésicas, antihipnóticas, desintoxicantes, antimicrobianas, bioenergéticas y biosintéticas. Por sus características atraumática, indolora, no invasiva, no provoca molestias ni efectos secundarios, lo que resulta en alta confiabilidad y cumplimiento por parte de los pacientes.(6) Existen 3 formas para aplicación local de ozono: el gas ozono, el agua ozonizada y aceite ozonizado.(7)

El aceite ozonizado es el resultado de la reacción del ozono con ácidos grasos y otras sustancias, este resultado de ozonización se consigue mediante el burbujeo de ozono en un generador del mismo. Durante esta reacción se forman sustancias como peróxidos, ozónidos, aldehídos, cetonas, entre otros.(8, 9) Los ozónidos cuando entran en contacto con exudados o heridas se descomponen y generan ozono, el cual se descompone generando peróxido de hidrógeno y lipoperoxidos que serían los responsables de los efectos regenerativos y desinfectantes. Esta liberación lenta de ozono además promueve el proceso de cicatrización al actuar como antimicrobiano local y promover la liberación de citoquinas con efecto reparador.(10)

Existen muchos estudios en la actualidad en la cual usan el aceite ozonizado como agente para el tratamiento de diferentes tipos de lesiones orales, mostrando mejores resultados en comparación a sus respectivos tratamientos convencionales en términos de menor tiempo de curación, mayor confort de los pacientes y ausencia de efectos adversos (5, 11-22), pero no existe un consenso acerca de su uso, acerca de sus beneficios ni tiempo de tratamiento. En base a eso el objetivo del presente estudio fue

realizar una RS del efecto terapéutico del aceite ozonizado sobre las lesiones orales en comparación con los tratamientos convencionales según cada tipo de lesión oral.

II. MATERIALES Y MÉTODOS

PROTOCOLO Y REGISTRO

Esta RS de acuerdo con el Informe Transparente de Revisiones Sistemáticas y Metanálisis – Declaración PRISMA.(23) El protocolo de revisión se registró en el Registro Internacional prospectivo de revisiones sistemáticas (PROSPERO) (número de registro CRD42021237068).

PREGUNTA FOCO

Las preguntas enfocadas a abordar fueron:

1. ¿Es eficaz el uso de aceite ozonizado en el tratamiento de lesiones ulceradas de la mucosa bucal?
2. ¿Es eficaz el uso de aceite ozonizado en el tratamiento de lesiones del hueso alveolar?

CRITERIOS DE ELEGIBILIDAD

Los criterios de inclusión para esta RS fueron los siguientes: Estudios clínicos que utilizaron aceite ozonizado como tratamiento de diferentes lesiones orales (estomatitis subprotésica, estomatitis aftosa recurrente, gingivoestomatitis herpética, pericoronaritis, alveolitis y gingivitis fibroedematosa). Se excluyeron revisiones de literatura, cartas al editor, comunicaciones breves, informes de casos, estudios piloto y ensayos que analicen otras aplicaciones del aceite ozonizado no relacionadas con

lesiones orales.

ESTRATEGIA DE BÚSQUEDA

Dos revisores independientes (J.Y y J.A) realizaron búsquedas en las bases de datos MEDLINE (PubMed), Embase, Cochrane Library, Scielo y LILACS hasta marzo de 2021. La búsqueda se realizó sin restricciones de fechas ni de idioma. La estrategia de búsqueda se aplicó de la siguiente manera: PubMed: ("Aphthous stomatitis" OR "Dry Socket" OR "Pericoronitis" OR "Herpetic Stomatitis" OR "subprothetic stomatitis" OR "fibro edematous" OR "alveolitis" OR osteomyelitis OR "Aphthous Ulcer" O "Estomatitis aftosa" O "Osteítis alveolar" O "Gingivoestomatitis herpética" O "Herpes simple oral" O "lesión bucal" O "lesión bucal") Y ("aceite ozonizado" O "Ozonizado" O "ozonización" O "ozono" O "ozonizado" O "ozonoterapia" O "ozonoterapia" O "ozonización" O "oleozón" O "aceites vegetales" O "aceites vegetales" U "ozonización"). En adición, e examinaron electrónicamente la literatura gris en el Sistema de Información sobre Literatura Gris en Europa (<http://www.opengrey.eu>) y las bases de datos de Google Scholar, tal como recomiendan los altos estándares para revisiones sistemáticas (directrices AMSTAR) (24).

Finalmente, también se realizaron búsquedas manuales en la lista de referencias de los estudios incluidos para capturar posibles registros adicionales, como lo sugirieron Greenhalgh y Peacock (25).

RECOPIACIÓN, EXTRACCIÓN Y GESTIÓN DE DATOS

BÚSQUEDA Y SELECCIÓN DE ARTÍCULOS

Los títulos y resúmenes fueron revisados por dos revisores independientes (JY. y JA). Se obtuvieron y revisaron los textos completos de los estudios que parecían cumplir con

los criterios de inclusión. Se utilizaron puntuaciones Kappa (coeficiente Kappa de Cohen) durante la evaluación del texto completo para garantizar la elegibilidad y el nivel de acuerdo entre los revisores. Los desacuerdos se resolvieron mediante discusión y consulta a un tercer revisor (GM).

EXTRACCIÓN DE DATOS

Los estudios que cumplieron con los criterios de elegibilidad fueron procesados para la extracción de datos, este proceso fue realizado por dos investigadores independientes utilizando hojas de cálculo predefinidas. Los desacuerdos se resolvieron mediante discusión con un tercer revisor. En caso faltaran datos, se envió una solicitud a los autores por correo electrónico. Para cada estudio seleccionado se recogieron las siguientes variables: 1) características del estudio: autor, año de publicación, país, diseño del estudio (ensayo clínico aleatorizado y no aleatorizado); 2) datos demográficos: tamaño de la muestra, edad media (años) y sexo (masculino/femenino); 3) medidas de resultado: tiempo de curación, intervalo de aplicación y efectos adversos (presencia o ausencia).

RIESGO DE SESGO

Dos revisores (J.M.M y J.Y) evaluaron el riesgo de sesgo en los estudios seleccionados, utilizando la herramienta Cochrane de riesgo de sesgo, RoB 2 (versión 2, disponible en: <https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2>).

Los autores de esta RS decidieron evaluar el resultado relacionado con la "asignación a la intervención (el efecto por intención de tratar)" y se examinaron cinco dominios: sesgo que surge de la asignación al azar y el proceso de ocultamiento de la asignación, sesgo debido a desviaciones de las intervenciones previstas que involucraban

enmascaramiento de los participantes y nuestro equipo de investigadores, sesgo debido a datos de resultado faltantes, sesgo en la medición del resultado y sesgo en la selección del resultado informado. Basándonos en las respuestas a las preguntas de señalización y los algoritmos de esta herramienta, juzgamos que cada dominio tiene "bajo riesgo de sesgo", "algunas preocupaciones relacionadas con el riesgo de sesgo" o "alto riesgo de sesgo". Los estudios se categorizaron como de bajo riesgo de sesgo (todos los dominios tenían bajo riesgo de sesgo), alto riesgo de sesgo (uno o más dominios tenían alto riesgo de sesgo) y preocupantes (si uno o más dominios tenían algunas inquietudes). Las decisiones se resolvieron mediante discusión, consultando a un tercer asesor (G.M).

Los ensayos no controlados aleatorios se evaluaron mediante la herramienta ROBINS-I.(40) Cada ensayo no controlado se clasificó como sin información o con riesgo de sesgo bajo, moderado, grave o crítico. Los desacuerdos entre los revisores se resolvieron mediante discusión abierta. En caso de que no se pudiera llegar a un acuerdo, la decisión final la tomó otro coautor (GM).

Los siguientes dominios se evaluaron para no ensayos controlados aleatorios(40):

- . Preintervención

- Sesgo debido a confusión

- Sesgo en la selección de participantes en el estudio

- . En la intervención

- Sesgo en la clasificación de intervenciones

- . Post-intervención

- Sesgo debido a desviaciones de las intervenciones previstas

- Sesgo debido a datos faltantes

- Sesgo en la medición de resultados

Sesgo en la selección del resultado informado

Para demostrar el riesgo general de sesgo, cada estudio incluido se clasificó como bajo, moderado, riesgo grave y crítico de sesgo o ausencia de información según los siguientes criterios:

- . Bajo riesgo de sesgo: se considera que el estudio tiene un bajo riesgo de sesgo para todos los dominios.
- . Riesgo de sesgo moderado: se considera que el estudio tiene un riesgo de sesgo bajo o moderado para todos los dominios.
- . Riesgo grave de sesgo: se considera que el estudio presenta un riesgo grave de sesgo en al menos un dominio, pero no tiene un riesgo crítico de sesgo en ningún dominio.
- . Riesgo crítico de sesgo: se considera que el estudio tiene un riesgo crítico de sesgo en al menos un dominio.
- . Sin información: no hay una indicación clara de que el estudio tenga un riesgo grave o crítico de sesgo y hay una falta de información en uno o más dominios clave de sesgo (se requiere un juicio para esto).

III. RESULTADOS

SELECCIÓN DE ESTUDIOS

La estrategia de búsqueda electrónica identificó 1957 artículos. Después de analizar los títulos y los resúmenes, se excluyeron 1932 estudios, los 25 restantes pasaron para una evaluación exhaustiva de texto completo, de los cuales fueron excluidos 12 por no cumplir con los criterios de elegibilidad. Por consiguiente 13 fueron el número de artículos incluidos en esta RS (Figura1).

CARACTERÍSTICAS DE LOS ESTUDIOS

Los trece ensayos clínicos aleatorizados (5, 11, 12, 14, 16, 18-20) y no aleatorizados (13, 15, 17, 21, 22) incluidos se realizaron entre 2010 y 2020, y se presentan sus principales características metodológicas en la Tabla 1. Todos los estudios clínicos mostraron el resultado efectivo del aceite ozonizado en diferentes tipos de lesiones orales: estomatitis subprotésica, estomatitis aftosa recurrente, gingivoestomatitis herpética, pericoronitis, alveolitis y gingivitis fibroedema; y utilizado como control el tratamiento convencional para cada tipo de lesión bucal. Un total de 1.644 pacientes de diferentes grupos etareos fueron incluidos en la presentes RS. Participantes en 3 estudios que padecían de pericoronitis (11, 12, 22), participantes de otros 3 estudios desarrollaron alveolitis (5, 18, 22), 5 estudios fueron desarrollados en pacientes con estomatitis aftosa recurrente (14, 16, 19, 21, 22), 3 estudios basados en estomatitis subprotésica (15, 17, 22), 2 estudios se basaron en pacientes con gingivitis fibroedematosa (20, 22), por último, un solo estudio contempló el uso de aceite ozonizado para pacientes con gingivoestomatitis herpética (13). Todos los estudios emplearon como terapia el uso local del aceite ozonizado. El período de seguimiento varió desde las 72 horas hasta las 6 semanas, dependiendo del tipo de lesión.

ACEITE OZONIZADO EN PERICORONARITIS

En 2 ensayos clínicos aleatorizados (ECA) (11, 12) y 1 no ECA (22) los autores informaron el uso del aceite ozonizado como terapia para la pericoronitis y lo compararon con la terapia convencional que consiste en ácido tricloroacético al 50% y enjuagues bucales con clorhexidina 0,2% por un periodo de tiempo entre 3 a 7 días, un intervalo de aplicación fue de 3 a 4 veces al día, con un tiempo de curación entre 72 horas y 7 días, un mayor número de pacientes se recuperaron en menor tiempo en el grupo de estudio (aceite ozonizado), mientras que en el grupo control mostró menores índices de satisfacción en el mismo

período de tiempo, mostrando diferencias estadísticamente significativas. No se informaron efectos adversos.

ACEITE OZONIZADO EN ALVEOLITIS

En 2 ECA (5, 18) y 1 no ECA (22), se utilizó el tratamiento con aceite ozonizado como tratamiento para la alveolitis y se comparó con alvogyl. Todos los estudios tuvieron un período de seguimiento de 7 días, intervalo de tiempo en el que se produjo la curación. Los tiempos de cicatrización de las lesiones fueron heterogéneos, variando entre 4 días (18), 5 días (5) o hasta 7 días (22) para el grupo de estudio (aceite ozonizado), el intervalo de aplicación varió desde 4 veces al día (22) hasta a cada 72 horas (5), no se informaron efectos adversos. En todos los casos, se observó un tiempo de recuperación más corto cuando se utilizó aceite ozonizado como terapia. Sin embargo, sólo un estudio (5) informó diferencias estadísticamente significativas.

ACEITE OZONIZADO EN GINGIVITIS FIBROEDEMÁTOSA

Sólo 2 estudios: 1 ECA (20) y 1 no ECA (22), utilizaron terapia con aceite ozonizado para la gingivitis fibroedematosa y se comparó con el uso de enjuagues bucales con clorhexidina al 0,2%, el tiempo de curación varió entre 7 días (22) y 6 semanas (20), mostrando solo resultados favorables en el grupo de estudio (en el cual el 96,6% de los pacientes sanaron), el intervalo de aplicación varió de 4 veces al día (22) a 2 veces a la semana (20), no se informaron efectos adversos. En ambos estudios hubo un tiempo de curación más corto cuando se usó el aceite ozonizado.

ACEITE OZONIZADO EN ESTOMATITIS SUBPROTÉSICA

Tres (15, 17, 22) de los estudios incluidos en esta RS (no ECA) utilizaron aceite ozonizado como tratamiento de la estomatitis subprotésica y lo compararon con el tratamiento convencional consistente en nistatina. El tiempo de seguimiento osciló entre 7 días (17, 22) y 15 días (15), por otro lado, el intervalo de aplicación del aceite ozonizado para este tipo de lesiones varió desde una vez al día (15, 17) hasta 2 veces al día (22). El tiempo de curación encontrado en los estudios varió desde 7 días (17, 22) hasta 12 días (15). En todos los estudios, hubo un tiempo de recuperación más corto cuando se utilizó aceite ozonizado como terapia en comparación con el tratamiento con nistatina. No se informaron efectos adversos.

ACEITE OZONIZADO EN ESTOMATITIS AFTOSA RECURRENTE

En 3 estudios ECA (14, 16, 19) y 2 estudios no ECA (21, 22), el aceite ozonizado se utilizó para tratar la estomatitis aftosa recurrente y lo comparó con otras terapias como: multivitaminas y enjuagues bucales con clorhexidina al 0,2% (14, 19), enjuagues bucales alcalinos de perborato de sodio y clorhexidina al 0,2% (16, 22), y finalmente un estudio comparativo con gel de metronidazol (21), con un tiempo de seguimiento que oscila entre 7 (14, 16, 19, 22) y 14 días. (21), un intervalo de aplicación de entre 2 (14, 19, 22) a 4 (16, 21) veces al día, como tiempo de curación entre 5 (14) y 7 días (16, 19, 21, 22). En todos los casos, se observó un tiempo de recuperación más corto cuando se empleó el aceite ozonizado como terapia. Sólo 2 estudios (19, 21) informaron diferencias estadísticamente significativas. No se informaron efectos adversos.

ACEITE OZONIZADO EN GINGIVOESTOMATITIS HERPÉTICA

Sólo 1 estudio(13) incluido en la presente RS empleó el aceite ozonizado como terapia para la gingivoestomatitis herpética y la compararon con el uso de iodoxuridina al 0.1% con un período de seguimiento de 10 días, el tiempo de curación fue ≤ 8 días para el grupo control, el intervalo de aplicación fue de 1 vez al día, no especificaron la presencia o no de efectos adversos. Los pacientes tratados con el aceite ozonizado tuvieron un menor tiempo de cicatrización de la lesión.

RIESGO DE SESGO DE LOS ESTUDIOS SELECCIONADOS

En los ECA, se encontraron métodos inadecuados de generación de secuencias y asignación de participantes en casi todos los artículos incluidos (90%) y solo un estudio mostró un proceso de asignación al azar correcto entre los grupos (Figura 2). En las desviaciones de las intervenciones previstas, el 60% de los estudios se clasificaron como "altos" debido a problemas con el enmascaramiento (Figura 3). Sin embargo, no fue posible enmascarar a todo el personal debido al contexto experimental. Finalmente, todos los estudios informaron los resultados sin un plan preespecificado. En general, se consideró que sólo un estudio tenía un riesgo de sesgo poco claro. En las Figuras 2 y 3 se muestra un resumen de los resultados del sesgo.

Tres de los estudios no ECA se clasificaron como con riesgo de sesgo severo (15-17), un estudio con riesgo de sesgo moderado (21) y un estudio se clasificó como con riesgo de sesgo crítico (13) como se muestra en la Figura 4.

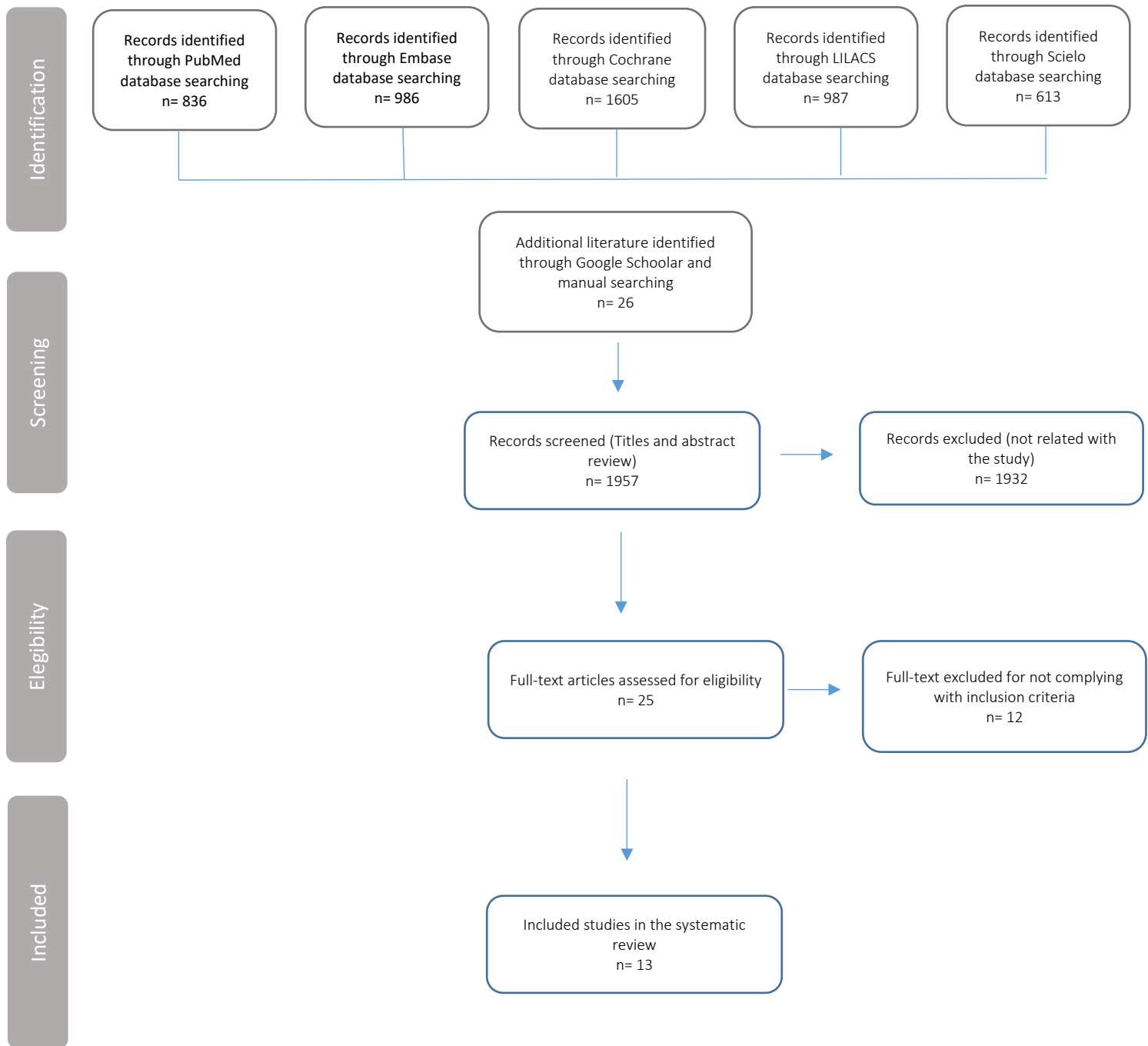


Figura 1. Diagrama de flujo de manuscritos seleccionados a través del proceso de revisión.

	D1	D2	D3	D4	D5	Overall	
Peña et al; 2019	-	-	+	!	-	-	+ Low risk
Leal et al; 2019	-	-	+	+	!	-	! Some concerns
Souto et al; 2018	-	!	+	-	!	-	- High risk
Diaz et al; 2018	-	-	+	-	!	-	
Fontaine et al; 2016	-	+	+	-	!	-	D1 Randomisation process
Martinez et al; 2015	+	+	+	+	!	!	D2 Deviations from the intended interventions
Mayor et al; 2011	-	-	+	-	-	-	D3 Missing outcome data
Mayor et al; 2010	-	-	+	-	-	-	D4 Measurement of the outcome
							D5 Selection of the reported result

Figura 2. Resumen del riesgo de sesgo de los ensayos clínicos incluidos en la revisión sistemática, según la herramienta Cochrane de riesgo de sesgo, RoB 2.

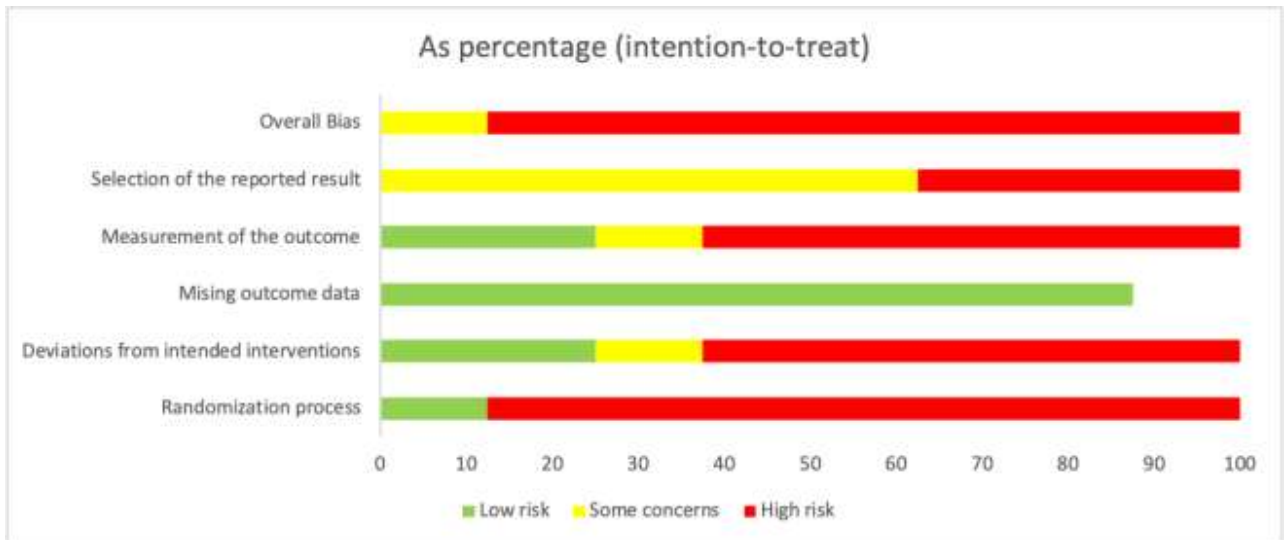


Figura 3. Resumen del riesgo de sesgo como porcentaje de los ensayos clínicos incluidos en la revisión sistemática.

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Alexandrina et al; 2020	+	?	-	+	+	+	+	-
Díaz et al; 2020	+	+	-	+	+	×	+	×
Jimenez et al; 2018	+	+	×	+	+	×	+	×
Castillo et al; 2018	+	+	-	×	+	×	+	×
Rodríguez et al; 2012	+	+	-	-	+	!	+	!

Domains:
 D1: Bias due to confounding.
 D2: Bias due to selection of participants.
 D3: Bias in classification of interventions.
 D4: Bias due to deviations from intended interventions.
 D5: Bias due to missing data.
 D6: Bias in measurement of outcomes.
 D7: Bias in selection of the reported result.

Judgement

- Critical
- Serious
- Moderate
- Low
- No information

Figura 4. Resumen del riesgo de sesgo de los ensayos clínicos no aleatorizados incluidos en la revisión sistemática, según la herramienta ROBINS-I.

Tabla1. Principales características de los estudios incluidos

Autor y año	Diseño	N	Edad	Sexo (M/F)	Tipo de lesión oral	Grupo control (GC)	Parámetros Evaluados	TS	IA	TC GE/GC	EA	Resultados
Mayor y col. 2010	ECA	90	> 15	25/65	pericoronaritis	ácido tricloroacético al 50%	Evaluación clínica: satisfactoria (mejora o cura a las 72h), insatisfactorio (igual o peor a las 72h). Eficacia del medicamento en estudio: buena (evolución clínica satisfactoria), mala (evolución clínica insatisfactoria)	72h	3 veces al día	72h/>72h	no	100% de eficacia buena del GE (AO), 62% de eficacia buena y 38% de eficacia mala en el GC (ácido tricloroacético)
Mayor y col. 2011	ECA	90	> 15	No específica	pericoronaritis	ácido tricloroacético al 50%	Evaluación microbiológica: satisfactoria (campo ausente o escaso, no predominan Gram -), insatisfactorio (campo abundante o campo cubierto, predominan Gram-). Grado de satisfacción de los pacientes (satisfecho y no satisfecho, según apreciación del paciente) y efectos adversos (si o no)	72h	3 veces al día	72h/>72h	no	Evaluación microbiológica, GE satisfactorio en 43 pacientes (96%), GC satisfactorio en 18 pacientes (40%). Satisfacción del paciente, satisfactorio: GE 43 pacientes (96%), GC 30 pacientes (66%).
Rodriguez y col. 2012	No ECA	250	<9	82/168	Gingivostomatitis herpética	iodoxuridina al 0.1%	Evolución: Curados: Cuando no existen signos clínicos de Gingivostomatitis Herpética Aguda. No curados: Cuando en la cavidad bucal existan signos clínicos de Gingivostomatitis Herpética Aguda	10d	1 vez al día	≤8d/8a-10d	no	79 pacientes tratados con AO (63.2%) curados en < 6 días, 78 pacientes tratados con iodoxuridina (62.4%) se curaron en 9 a 10 días, el tratamiento con AO minimiza el tiempo de cicatrización.
Martinez-Abreu y col. 2015	ECA	100	20-59	56/44	Alveolitis	Alveogil	Clínico: recuperado (dolor e inflamación desaparecen), mejorado (dolor e inflamación disminuyen), igual (dolor mantiene intensidad e inflamación persiste), peor (dolor e inflamación persisten o empeoran). Microbiológico: infectado (presencia de m.o. piógenos), libre de infección (ausencia de m.o. piógenos)	7d	c/72h	3a4 días/>3,4 días	no específica	100 pacientes en 2 grupos: 50 GE (AO) y 50 GC (alveogil) Se evaluaron a los pacientes a las 72h (2da visita), 96h (3era visita) y a la semana de tratamiento (4ta visita). 41 pacientes del GE sólo

							evaluación de la Eficacia: bueno (criterio clínico de recuperado y microbiológico libre de infección), aceptable (criterio clínico de mejorado y microbiológicos libre de infección) y malo (criterio clínico de igual o peor y microbiológico infectado).					necesitaron 2 visitas para recuperarse, GC sólo 29 pacientes. Para la evaluación microbiológica: de 20 pacientes en el GE 13 pacientes mostraron signos de libre de infección, mientras en el GC de 20 pacientes evaluados sólo 6 mostraron el mismo resultado.
Fontaine y col. 2016	ECA	80	> 12	26/54	estomatitis aftosa recurrente	vitaminas y colutorio con clorhexidina 0,2%.	Evaluación clínica: satisfactoria (disminuye el dolor o desaparece, disminuye el tamaño de la lesión o desaparece) no satisfactorio (persiste el dolor y no se aprecia cambios en la lesión). Curación: curado (no existen signos clínicos de estomatitis) y no curado (en la mucosa existen signos clínicos de estomatitis). Grado de satisfacción: satisfecho y no satisfecho (para ambos criterios se tuvo en cuenta la percepción de los pacientes).	7d	2 veces al día	4 a 5 días	no	GE y GC 40 pacientes cada uno. GE: 34 pacientes necesitaron sólo de dos a tres aplicaciones para considerar una evaluación clínica satisfactoria, 38 pacientes solo necesitaron como máximo de 4 a 5 días para considerarse curados. GC: 18 pacientes necesitaron más de 7 días. Grado de satisfacción: 97.5% del GE satisfechos.
Castillo y col. 2018	No ECA	68	>19	17/51	estomatitis subprotésica	nistatina	Evaluación clínica, la curación se determinó según desaparecía la lesión y se tornaba la mucosa fisiológica	15d	1 vez al día	4 a 12 días	no	GC la mucosa alcanzó la normalidad entre 10 a 12 días (52.9% de la muestra). Solo el 14,7% lo logro entre 7 y 9 días; ningún paciente logro su curación durante la primera semana de

												tratamiento.
												GE el 44.1% de pacientes alcanzó la normalidad de la mucosa entre 7 a 9 días, el 32.4% alcanzó normalidad entre 4 a 6 días. El 76.6% de los pacientes del GE curaron antes de los 10 días de aplicación.
Díaz-Couso y col. 2018	ECA	32	> 12	12/20.	estomatitis aftosa recurrente	colutorios alcalinos de perborato de sodio y colutorios de clorhexidina al 0,2 %	Curado , existe buen estado general de la zona afectada (remisión de los síntomas) y desaparición de la úlcera. No curado , permanencia de la úlcera, no remite los síntomas con la aplicación del medicamento. Para el criterio de reacciones adversas, se tuvo en cuenta la presencia en la zona afectada de ardor, rubor, calor, tumor y dolor.	7d	4 veces al día	3 a 7 días en ambos grupos	no	Al tercer día en el GE evolucionaron favorablemente ocho pacientes (50 %) y en el GC el 12, 5 %. En general la evolución del tratamiento, pacientes curados: GE 93,7 % y GC 68,7 %.
Jimenez y col. 2018	No ECA	40	> 20	17/23	estomatitis subprotésica	nistatina	Efectividad del tratamiento: Muy efectivo, efectivo y poco efectivo.	7d	1 vez al día	4 a 7 días	no	Evaluación de la efectividad del tratamiento en la estomatitis subprótesis: GE, tratamiento efectivo en 14 pacientes (35,0 %), GC tratamiento poco efectivo con 18 pacientes (45,0 %). La aplicación diaria del AO fue efectiva para el tratamiento de esta enfermedad entre cuatro y siete visitas a consulta,

												tiempo de curación fue menor en comparación a la nistatina en crema en el GC.
Souto y col. 2018	ECA	100	20-59	No específica	alveolitis	alveogil	Dolor (referido por el paciente al inicio y posterior a la aplicación de los tratamientos a los 5, 15, y 30 minutos, escala analógica visual) Inflamación (estado de la mucosa que rodea al alveolo, por observación directa: inflamada (hipercolorada, aumento de volumen, lisa); ligeramente inflamada (ligeramente hipercolorada y ligero aumento de volumen) y no inflamada (normalmente coloreada, resiliente y tamaño normal). Cicatrización: no cicatrizado (retraso en la formación del coagulo, fetidez, hipersensibilidad en las paredes del alveolo), cicatrización parcial (a pesar de la neoformación del coagulo, presenta hipersensibilidad, ligera fetidez) y cicatrización total (alveolo ocupado por un coagulo sanguíneo nuevo, con formación de tejido de granulación y proliferación del epitelio en la superficie externa). Respuesta al tratamiento: sin respuesta al tratamiento (paciente igual, no desaparece el dolor, no hay formación del coagulo, paredes del alveolo hipersensibles y fetidez), mejorado (dolor no intenso, ligera fetidez y neo formación del coagulo) y curado (desaparece el dolor, coagulo formado y formación de tejido de granulación).	7d	1 sola aplicación	4 a 5 días	No específica	Dolor: GE, 40 pacientes (80 %) no referían dolor a los 5 minutos de aplicado el AO. GC, 13 pacientes no referían dolor a los 5 minutos de aplicado el medicamento, hubo diferencias estadísticamente significativas. Grado e inflamación: GE, 40 pacientes con inflamación a las 96 horas después de aplicado el tratamiento, sin embargo, no hubo diferencias estadísticamente significativas. Cicatrización: GE, 46 pacientes (92%) cicatrizaron a las 96h. GC, 44 pacientes cicatrizados (88 %) Respuesta al tratamiento: 86% del GE resultó curado a las 96h y 80% del GC en el mismo tiempo,

Leal-Rodríguez y col. 2019	ECA	120	15-35	40/80	estomatitis aftosa recurrente	vitaminas, difenhidra-mina y colutorio con clorhexidina 0,2%.	Se evaluaron desde el punto de vista clínico el estado de las lesiones y todos los datos referidos al tiempo de evolución, para establecer el diagnóstico e instaurar el tratamiento	7d	2 veces al día	7d / >7d	no	La evaluación al séptimo día: GE, 93,33 % curaron. GC solo 56,67 % evolucionaron satisfactoriamente. Por lo tanto, el tiempo necesario para desaparecer los signos clínicos de la enfermedad fue menor cuando se aplicó el AO que cuando se aplicó el tratamiento convencional.
Peña y col. 2019	ECA	60	> 15	No específica	gingivitis crónica fibroedematosa	colutorios con clorhexidina 0,2%	Se evaluaron desde el punto de vista clínico el estado de las lesiones: curado, mejorado, igual o empeorado	6sem	2 veces por semana	6 sem	no	En ambos grupos la mayoría de los pacientes evolucionó satisfactoriamente en las 2 primeras semanas de tratamiento. GE luego de la cuarta visita o semana de tratamiento, se observó clínicamente la resolución de todos los síntomas de inflamación al 70% de los pacientes, mientras que en el GC al 56,6%. En la sexta semana en el GE el 96,6% de los casos se emitió criterio de curación, mientras que en el GC al 90 %.
Alexandrina y col. 2020	No ECA	30	No específica	No específica	estomatitis aftosa recurrente	Metrogildenta gel (metronidazol 10mg)	Examen clínico, incluyendo una encuesta, aclaración de quejas y un examen visual. Para más detalle, utilizaron un estudio bacterioscópico CITO.	14d	4 veces al día	3 a 7 días en ambos grupos	No específica	En comparación con el tratamiento dental tradicional, se notó la ventaja

de utilizar AO, al segundo día después del tratamiento, los pacientes informaron una disminución del dolor. Menos efectivo fue el método de irrigación con oxígeno-ozono. Los sujetos del tercer grupo, que fueron tratados con aplicaciones de Metrogil Denta, mostraron los peores resultados y se observó una mejoría clínica entre los 6 y 7 días posteriores al tratamiento.

Díaz-Couso 2020	No ECA	464	> 12	215/249	Alveolitis, estomatitis subprotésica, gingivitis crónicas fibromatosa, estomatitis aftosa recurrente, pericoronaritis	Estomatitis subprotésica (Nistatina), estomatitis aftosa recurrente (colutorios alcalinos de perborato de sodio y enjuagatorios antisépticos de clorhexidina al 0,2%), alveolitis (alveogil), Pericoronaritis (clorhexidina al 0,2%). Gingivitis crónica edematosa	La efectividad del tratamiento se tuvo en cuenta mediante su evolución favorable o no al tratamiento durante siete días, remisión de los síntomas y/o desaparición de la enfermedad. Para el criterio de reacciones adversas se tuvo en cuenta la presencia en la zona afectada de ardor, rubor, calor, tumor y dolor.	7d	2 veces al día	7d / >7d	no	Al tercer día, GE evolucionaron favorablemente e 97 pacientes (41,8 %); ya al séptimo día sumaban 209 pacientes (90,1 %). GC al tercer día solo el 26,2 % habían evolucionado favorablemente, creciendo hasta el 53,3 % al quinto día. Se observó que al séptimo día había ausencia total de dolor y remisión de todos los síntomas de las enfermedades bucales en un mayor número de pacientes, pertenecientes al GE. La autora considera que el tratamiento con AO ayudó a
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(colutorios de clorhexidina al 0,2 %)

la recuperación en menor intervalo de tiempo a los pacientes y casi todos remitieron los síntomas y signos presentados antes de los primeros siete días. No se presentaron reacciones adversas durante el tratamiento.

ECA: ensayo clínico aleatorizado, No ECA: ensayo clínico no aleatorizado, N: número total de participantes, M: masculino, F: femenino, TS: tiempo de seguimiento, d: tiempo en días, h: tiempo en horas, IA: intervalo de aplicación, GE: grupo de estudio, GC: grupo control, TC: tiempo de curación, EA: efectos adversos

Tabla 2. Estudios excluidos y la razón de su exclusión.

AUTOR (AÑO)	TÍTULO DEL ARTÍCULO	RAZÓN DE LA EXCLUSIÓN
Soler y col (2020)	Application of ozonated sunflower oil in patients affected with chronic fibroedematous gingivitis	No presenta grupo control
Frías y col (2020)	Effectiveness of ozone therapy in the treatment of sub-prosthesis stomatitis in Manzanillo 2018-2019.	No presenta grupo control
Céspedes y col (2019)	Usefulness of topical Oleozón® in oral ulcers in patients with mechanical artificial ventilation	No se compara con terapia convencional
Télles y col (2018)	Use of oleozón® in sub-prosthetic stomatitis	No presenta grupo control
Jorge y col (2017)	Effectiveness of oleozón in the treatment of sub-prosthetic stomatitis in patients over 60 years of age.	No presenta grupo control
Casado y col (2017)	Effectiveness of oleozon treatment versus aloe vera cream in subprosthetic stomatitis	No se compara con terapia convencional
Al-Omiri y col (2016)	Ozone treatment of recurrent aphthous stomatitis; a double blinded study	No presenta grupo control
Kumar y col (2016)	Efficacy of Ozonated olive oil in the management of oral lesions and conditions: a clinical trial	No presenta grupo control
Milanés y col (2016)	Ozone therapy in sub-prosthesis stomatitis, 2016	No presenta grupo control
Armas y col	Efficacy of two natural therapies in the	No se compara con terapia

(2015)	remission of pain in recurrent aphthous stomatitis	convencional
Báez y col (2015)	Ozone therapy in a patient with bucal sores	Reporte de caso
Colás-Costa y col	The effectiveness of oleozon in the treatment of recurrent aphthous stomatitis	No presenta grupo control

IV. DISCUSIÓN

En esta RS, se estudió el efecto terapéutico del aceite ozonizado en lesiones orales como la estomatitis subprotésica, estomatitis aftosa recurrente, gingivoestomatitis herpética, pericoronaritis, alveolitis y gingivitis fibroedematosa, para poder diferenciarlas se hizo un análisis por cada tipo de lesión oral y su respectivo tratamiento convencional, sin embargo a pesar de las diferencias que existen en cada tipo de lesión oral siempre se encontró un efecto terapéutico positivo respecto al uso del aceite ozonizado cuando se lo comparó con el tratamiento convencional respectivo, este efecto se vio reflejado en muchos casos como un menor tiempo de tratamiento o un mayor confort por parte del paciente. Otro punto a favor encontrado en la mayoría de los estudios incluidos fue la ausencia de efectos adversos, mostrándose como una terapia segura para los pacientes.

Con respecto a la pericoronaritis, Wehr y col.(28) en una reciente RS acerca del estándar de atención de la pericoronaritis basado en evidencia, informaron que recetar antibióticos y programar una cita de seguimiento era la opción de tratamiento más común para estos casos; no obstante los 3 estudios relacionados a este evento incluidos en la presente RS usan el ácido tricloroacético y colutorios de clorhexidina al 0,2% y lo comparan con el uso local del aceite ozonizado, mostrando este último tiempos de resolución más cortos(11, 12).

El alveogil es un producto que se ha usado para poder comparar su efecto con otros productos como tratamiento para la alveolitis, esto después de que Alexander(29) y Bloomer(30) lo recomendaran para ese tipo de casos; sin embargo, esta RS muestra superioridad del aceite ozonizado respecto a dicho producto con resultados positivos en menor tiempo. Cabe mencionar que otros estudios ya mostraban otros productos con mejores resultados que el alveogil, Taberner y col(31) en una RS sobre los métodos usados para el manejo de la alveolitis seca, recomiendan la terapia laser, óxido de zinc eugenol y el plasma rico en factores de crecimiento; por otro lado, surge el aceite ozonizado como una alternativa más simple que el láser o el plasma rico en plaquetas, que involucra un menor costo e inclusive el mismo paciente podría usar en casa.

Con respecto a la gingivitis fibroedematosa, Gawron y col(32) mencionan en su revisión que el tratamiento de rutina de este tipo de lesiones cuando es un agrandamiento mínimo y local se basa en mantener una higiene bucal adecuada y realizar un raspaje y alisado radicular, mientras que para casos en los cuales se presenta un agrandamiento gingival difuso y avanzado, requiere posiblemente hasta una intervención quirúrgica, indicando en todos los casos colutorios con clorhexidina, así mismo recomienda investigar métodos terapéuticos menos invasivos. En la presente RS, existen 2 estudios(20, 22) en los cuales el aceite ozonizado, combinado con una buena higiene oral, obtuvo resultados favorables y en menor tiempo en comparación con el uso de clorhexidina, esto podría deberse al gran efecto antibacteriano que posee el aceite ozonizado reportado en algunos estudios microbiológicos(33, 34) donde el potencial de acción del aceite ozonizado para patógenos periodontales y otras bacterias oportunistas es igual o mayor al de la clorhexidina.

El tratamiento para la estomatitis subprotésica es regularmente la nistatina, la cual ha

demostrado eficacia para su tratamiento en diversos estudios(35), sin embargo, a pesar que se tenga buenos resultados, 3 estudios incluidos en esta RS que compararon el uso de nistatina con el aceite ozonizado(15, 17, 22) lograron recuperación en un menor intervalo de tiempo, hay que recordar que el aceite ozonizado no sólo tiene propiedades antimicrobianas y anti fúngicas, sino también estimulan el sistema inmune y promueve la cicatrización de heridas(36).

La estomatitis aftosa recurrente es la lesión más común en la mucosa oral, aunque su historia natural es curarse sin ninguna secuela, las formas más severas muchas veces necesitan tratamiento enfocado a la reducción del dolor y la promoción de la cicatrización de las úlceras (8,12). Los corticoides son normalmente usados, así como la aplicación tópica de clorhexidina, tetraciclina y peróxido de hidrógeno diluido(37, 38). A pesar que no existe evidencia del origen bacteriano de la estomatitis aftosa recurrente, en esta RS los 5 estudios que involucraron este tipo de lesión(14, 16, 19, 21, 22), en su gran mayoría comparan el uso del aceite ozonizado con clorhexidina local y suplementos vitamínicos vía oral, éstos al ser comparados con el aceite ozonizado necesitaron de más tiempo de recuperación. Estos resultados podrían asociarse a las propiedades antimicrobianas y de cicatrización que posee el aceite ozonizado(36), dándole la ventaja.

La gingivoestomatitis herpética es una lesión oral común en niños y aunque normalmente se trata de controlar la sintomatología y el tratamiento asignado es Aciclovir (39, 40), en el estudio incluido en esta RS usan otro antiviral la iodoxuridina, la cual al compararla con el aceite ozonizado tuvo un mayor tiempo de recuperación; a pesar de que no existe evidencia de alguna propiedad antiviral del aceite ozonizado, sus propiedades que promueven y mejoran la cicatrización(36) permiten una rápida recuperación una vez haya pasado el ciclo

viral de dicha enfermedad.

En esta RS hubo diversidad de información y metodología de los estudios incluidos que no permitieron realizar un metanálisis. La mala metodología se reflejó en el alto riesgo de sesgo. Por lo tanto, los autores sugieren que es necesario realizar más estudios clínicos con mayores estándares de rigor metodológico. Sin embargo, a pesar de las diversas presentaciones en los estudios seleccionados, se pudo observar ventajas para el uso del aceite Ozonizado en el tratamiento de lesiones bucales, logrando una curación más rápida y ausencia de efectos adversos. En consecuencia, los autores sugieren que el uso del aceite de ozono debe ser ampliamente divulgado en la comunidad odontológica y el mundo científico, para que tenga un futuro prometedor en diferentes tipos de tratamiento en nuestra especialidad.

V. CONCLUSIONES

En resumen, los resultados de esta RS, a pesar de la poca información encontrada y de la falta de rigor metodológico de los estudios incluidos, sugieren un efecto positivo respecto al uso del aceite ozonizado para el tratamiento de lesiones orales, así mismo cuando se comparó ese efecto con otros tipos de tratamientos usados de manera cotidiana en los diversos tipos de lesiones orales se encontró ventaja en términos de menor tiempo de curación y no se reportaron efectos adversos, mostrándose como un tratamiento seguro y confiable para los pacientes.

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ABREVIATURAS

LILACS: Literatura Latinoamericana y del Caribe en Ciencias de la Salud

Non- RCT: Ensayo Clínico no Aleatorizado

RCT: Ensayo Clínico Aleatorizado

RS: Revisión Sistemática

ANEXOS

ODOVTOS

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LITERATURE REVIEW

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Is the Use of Ozonated Oil Effective in the Treatment of Oral Lesions? Systematic Review of Clinical Studies

¿Es el uso del aceite ozonizado efectivo en el tratamiento de las lesiones orales? Una revisión sistemática de estudios clínicos

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ABSTRACT: The aim of this study was to perform a systematic review (SR) of the therapeutic effect of ozonated oil for oral lesions treatment. A SR was conducted according to the PRISMA guidelines. The Medline (PubMed), Embase, Cochrane Library, Scielo and LILACS were investigated, together with manual searches, to extract all publications until December 2020, including randomized and non-randomized clinical trials reporting the effects of ozonated oils on the management of oral lesions when compared with other methods. The risk of bias (RoB) of the studies included were assessed by using the RoB 2 tool and ROBINS-I. After analyzing the titles and reading the abstracts, 1932 articles were excluded; the remaining 25 passed a full-text evaluation. Ultimately, 13 articles were included in this SR. There was heterogeneity of the results regarding healing times and intervals of ozonated oil application for the treatment of each type of oral lesion, but in general, there was a shorter healing time when ozonated oil was used as therapy, and no adverse effects were reported. Despite the limited information found and the lack of rigorous methodological standards for the use of ozonated oil on oral lesions, a positive effect was suggested. The findings indicated an advantage in terms of shorter healing times when compared with other

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COMITÉ INSTITUCIONAL DE ÉTICA EN INVESTIGACIÓN



CONSTANCIA N° 85-CIEI-CIENTÍFICA-2021

El presidente del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur (CIEI-CIENTÍFICA) da constancia que el proyecto de investigación, cuyos datos se registran a continuación, ha sido **aprobado** por el CIEI-CIENTÍFICA.

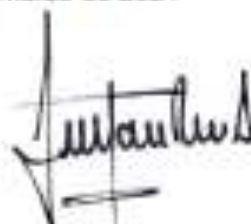
Código de registro: **548-2020-POS8**
 Título: **El aceite ozonizado en el tratamiento de lesiones orales: una revisión sistemática**
 Investigador(a): **Josef Yábar Condori**

La aprobación del proyecto de investigación implica que el documento presentado a evaluación cumple con los lineamientos de Universidad en materia de investigación y ética, los cuales se sustentan en la normativa internacional vigente. Adicionalmente, en el contexto de la pandemia de enfermedad por COVID-19, le recomendamos cumplir con las normas publicadas por el estado peruano (accesos, medidas de bioseguridad, etc.) y tener los permisos de las instituciones en las que realizará el estudio antes de ejecutarlo.

En tal sentido, esta aprobación carecerá de valor si es que el proyecto de investigación arriba indicado es modificado de cualquier forma. Toda enmienda, añadido, eliminación o eventualidad (eventos adversos, etc.) posterior a la fecha de aprobación debe ser reportado al CIEI-CIENTÍFICA.

La vigencia de la aprobación de este documento es de dieciocho (18) meses (**hasta el 17 de setiembre del 2022**), periodo en el que puede desarrollarse el proyecto. Cualquier trámite para su renovación deberá ser enviado antes del término de la vigencia de este documento, debiendo suspenderse todo desarrollo hasta que la renovación sea aprobada. La presente aprobación será ratificada en la sesión del CIEI más próxima.

Villa El Salvador, 18 de marzo de 2021




Mg. Fulton Paul Rivera Albinagorta
 Presidente
 Comité Institucional de Ética en Investigación

**RESOLUCIÓN DIRECTORAL DE ACEPTACIÓN DEL PROYECTO DE TESIS
Y NOMBRAMIENTO DEL ASESOR****RESOLUCIÓN DIRECTORAL DE LA CARRERA DE ESTOMATOLOGÍA N.º
010-DACE-DAFCS-U. CIENTÍFICA-2021**

Lima, 20 de abril del 2021

VISTO:

El informe técnico del Comité Institucional de Ética en Investigación de la Universidad Científica del Sur con código N.º 548-2020-POS99, se aprueba el proyecto de Tesis titulado: "EL ACEITE OZONIZADO EN EL TRATAMIENTO DE LESIONES ORALES: UNA REVISIÓN SISTEMÁTICA" presentado por JUSEF YABAR CONDORI.

CONSIDERANDO:

Que, de acuerdo al Reglamento General de la Universidad Científica del Sur y los reglamentos de pre/posgrado para obtener el Grado Académico de MAESTRO EN PERIODONCIA E IMPLANTES en la Carrera de Estomatología de la Universidad Científica del Sur, se debe desarrollar un trabajo de investigación.

Que, de acuerdo con la normativa vigente de la Universidad Científica del Sur, en uso de las atribuciones conferidas al Director Académico de Carrera.

SE RESUELVE:

ART. 1º: APROBAR E INSCRIBIR el Proyecto de Tesis titulado: "EL ACEITE OZONIZADO EN EL TRATAMIENTO DE LESIONES ORALES: UNA REVISIÓN SISTEMÁTICA" de el/la Bach. JUSEF YABAR CONDORI, con registro: N.º 548-2020-POS99 y establecer el inicio de periodo de ejecución del mencionado proyecto.

ART. 2º: NOMBRAR Asesor/a del trabajo de tesis señalado, a el/la Mg. Esp. GERARDO MENDOZA AZPUR.

Regístrese, comuníquese y archívese.



Dr. Claudio Peña Soto
Director Académico de la Carrera de Estomatología

