




ALTERNATIVE PRODUCTS IN TOPICAL TREATMENT OF RADIATION INDUCED XEROSTOMIA: A SYSTEMATIC REVIEW

Produtos alternativos no tratamento tópico da xerostomia radioinduzida: uma revisão sistemática

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ABSTRACT

Xerostomia, a term used to characterize the sensation of dry mouth, it is one of the most common symptoms after radiotherapy treatment of the head and neck region, being also the most expensive, impacting the oral health and quality of life of these patients. We performed a systematic review to identify topical treatments of natural composition in patients with radiation induced xerostomia. Searches were carried out in electronic databases such as the databases consulted were Cochrane library, PubMed (MEDLINE) and Latin American and Caribbean Literature in Health Sciences – LILACS. The research was carried out from June to July 2022 the period admitted for the results were from 1990 to 2022. We included trials of topical interventions with natural composition such, medicinal mucilage, sprays, oils and chewing gums for the management of dry mouth symptom. Results: 6 studies fully met the desired criteria, totalizing 336 patients. The therapies based on natural products were compared with placebo or other treatments and the forms of presentation were spray, oil, medicinal mucilage, and gel. In general, there was an improvement in some signs and symptoms of xerostomia and the most described adverse effect was nausea. Natural composition products seem to be a good alternative therapy for the relief of xerostomia symptoms and their consistency and form of application seem to exert influence, as evidence is still scarce, more randomized and placebo-controlled clinical studies are needed.

Keywords: Xerostomia; Head and neck cancer; Treatment; Herbal; Radiotherapy.

RESUMO

A xerostomia é o termo utilizado para caracterizar a sensação de boca seca, sendo um dos sintomas mais comuns após o tratamento radioterápico da região de cabeça e pescoço e também o mais oneroso, impactando na saúde bucal e na qualidade de vida desses pacientes. Realizamos uma revisão sistemática para identificar tratamentos tópicos de composição natural em pacientes com xerostomia induzida por radiação. As buscas foram realizadas em bases de dados eletrônicas, sendo que as bases de dados consultadas foram a biblioteca Cochrane, PubMed (MEDLINE) e Literatura Latino-Americana e do Caribe em Ciências da Saúde – LILACS. A pesquisa foi realizada de junho a julho de 2022, o período admitido para os resultados foi de 1990 a 2022. Incluímos ensaios de intervenções tópicos com composição natural como mucilagem medicinal, sprays, óleos e gomas de mascar para o manejo do sintoma de boca seca. Nos resultados 6 estudos preencheram



totalmente os critérios desejados, totalizando 336 pacientes. As terapias baseadas em produtos naturais foram comparadas com placebo ou outros tratamentos e as formas de apresentação foram spray, óleo, mucilagem e gel. Em geral, houve melhora de alguns sinais e sintomas da xerostomia e o efeito adverso mais descrito foi a náusea. Os produtos de composição natural parecem ser uma boa alternativa terapêutica para o alívio dos sintomas da xerostomia e sua consistência e forma de aplicação parecem exercer influência, como as evidências ainda são escassas, são necessários mais estudos clínicos randomizados e controlados por placebo.

Palavras-Chave: Xerostomia; Câncer de cabeça e pescoço; Tratamento; Ervas; Radioterapia.

INTRODUCTION

Xerostomia is defined as dry mouth and in some cases, it is referred by patients who do not necessarily present an objective sign of hyposalivation, being considered a secondary symptom to qualitative and/or quantitative alterations in the salivary composition (VILLA, CONNELL & ABATI, 2014). It is one of the most frequent symptoms reported by patients undergoing radiotherapy (RT) of the head and neck, in addition to being the costliest (ADA, 2021)

Exposure to salivary gland radiation results in a dramatic loss of function within the first week of treatment with a continuous decrease in salivary flow rate throughout therapy (MERCADANTE et al., 2016). The critical dose limit for parotid and submandibular salivary gland tissue is just under 40 Gy, and most radiation regimens exceed this limit. Irradiation leads to the loss of saliva-producing acinar cells and impairment of duct function with irreversible damage. Therefore, in these patients, therapies are considered palliative (JENSEN et al., 2010; JENSEN et al., 2019).

Multinacional Association of Supportive Care in Cancer (MASCC) in 2021 published a guide with recommendations and levels of evidence to treat or prevent xerostomia in cancer patients, among them; it cites the use of salivary substitutes and oral lubricants with a strong level of evidence. Some systemic drug treatments can generate discomfort and side effects to the point of not benefiting the xerostomic patient (MERCADANTE et al., 2021).

Some studies suggest that the antioxidant coenzyme Q10 increases the production of adenosine triphosphate (ATP) and thus activates secretory



capacity and water secretion mechanisms, resulting in increased salivary secretion (AITKEN-SAAVEDRA et al., 2020; LEE et al., 2021; ZHOU et al., 2015). Other natural extracts enriched with free radicals such as α -tocopherol, *Melaleuca alternifolia*, *Rhodiola rosea* L., *Portulaca oleracea*, xylitol, lycopene, urea and a wide range of phytoconstituents of *Ceratonia siliqua*, such as phenolic compounds, flavonoids, tannins, anthocyanins, alkaloids, glycosides, proteins and minerals showed nutritive, antioxidant, antibacterial, antifungal, analgesic, anti-inflammatory and, antiproliferative effects (CASARIN et al., 2018; LAKKAB et al., 2018; PU et al., 2020; SILVA et al., 2021). The objective of this work was to carry out a systematic review to identify whether an oral lubricating of alternative composition would be effective in relief radiation induced xerostomia.

METHODOLOGY

The present study is a systematic review that was performed in accordance with the “Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols” (PRISMA-P, 2015). 14. The search was performed using “MeSH” terms and keywords based on the elements of the PICO question:

1. Participants (P): Xerostomic patients
2. Intervention (I): Alternative topical products
3. Comparison or control (C): Other topical treatment
4. Outcome measures (O): Success of treatment to improve xerostomia

INFORMATION SOURCES AND SEARCH STRATEGY

An exhaustive search of the literature available in Cochrane library, PubMed (MEDLINE) and Latin American and Caribbean Literature in Health Sciences – LILACS until July 2022 was conducted. The following keywords were used in the search strategy: “xerostomia” OR “dry mouth” OR “dryness mouth” AND “treatment” OR “therapeutics” OR “topical drug administration” OR “herbal” OR “head-and-neck cancer” OR “radiotherapy” search terms are listed in appendix 1, relevant titles, abstracts published in Portuguese, English or Spanish from (1990-2022). The full title and abstract of each article were screened by two independent authors (G.S.A. and L.M.I.) using predetermined inclusion and exclusion criteria (Fig. 1). All of the references were selected from the EndNote X9 (Thomson Reuters, Philadelphia, PA, USA). Any differences in the selection



of the studies were resolved by discussion with a third reviewer (H.R.) (PAGE et al., 2021).

ELIGIBILITY CRITERIA

Inclusion criteria: clinical trials that compared topical treatments for radioinduced xerostomia that were formulated with alternative ingredients to a placebo or other treatment were considered for inclusion in Portuguese, English and Spanish.

Characteristics of the participants: participants with a history of radiotherapy treatment for cancer in the head and neck region, these patients suffered from treatment-induced chronic xerostomia

Types of intervention: topical treatments were considered for the management of xerostomia with a natural formulation in different forms of presentation, including sprays, medicinal mucilage, oils, chewing gums and gels.

Exclusion criteria: studies carried out during the radiotherapy period, products for systemic use and topical products that were not of alternative composition, studies with topical products of alternative composition used for the treatment of xerostomia induced by other factors and works published in other languages.

RESULTS

The search results are illustrated in Figure 1, with the sequence described in the form of a flow diagram. Included articles that fully met the criteria for this systematic review are described in Table 1. The electronic searches identified 1.517 references, from these, we initially excluded 1.441 articles, after we identified 76 reports of trials as eligible according to the title after reading abstract, and we excluded 52 articles. Of 24 articles that seemed to meet the inclusion criteria, 1 was excluded because it was repeated, 13 were excluded because they addressed other topics such as 3 acupuncture, 4 drugs parasympathomimetics, 1 use of hyperbaric oxygen, 1 therapy with mesenchymal cells, 2 transcutaneous electrical nerve stimulation, 2 surgical transfers of salivary glands and 1 photobiomodulation, 9 articles were assessed for eligibility, of which 6 studies fully met the desired criteria to systematic reviewed, totaling 336 patients.

All included trials were conducted in adult patients. Trials recruited between 10 and 123 participants, with a mean of 56 participants per trial, the lowest



recruitment was with 10 patients and the largest was with 123 patients. The mean ages were 59.12 years.

The identified works generally evaluated the signs and symptoms related to xerostomia in the short term during the period of use of the proposed therapies. The signs were evaluated using a visual analog scale (VAS) that analyzed isolated or non-isolated aspects of xerostomia such as daytime dryness, speech difficulties and swallowing difficulties.

The symptoms of xerostomia were evaluated through the application of xerostomia questionnaires. The acceptability and preference of the products were evaluated through the application of questionnaires. The assessment of the health of the oral structures was evaluated through plaque and gingival bleeding indices.

The therapies based on alternative products were compared with placebo or other treatments and the forms of presentation were spray, medicinal mucilage, chewing gums oil and gel. In general, there was an improvement in some signs and symptoms of xerostomia and the majority described adverse effects were nausea, vomiting, burning mouth and epigastric pain. One study was controlled by an arm where patients received routine hydration care and compared to the experimental group where patients used chewing gum (KAAE et al., 2020). One study consisted only of patients using the experimental product Salix STT (SENAHAYAKE, PIGGOTT & HAMILTON-MILLER, 1998) In total were reported 38 dropouts.

In total, 248 men and 88 women were evaluated. Radiotherapy was applied at doses ranging from 40 - 70 Gy to treat 197 tumors in the oral cavity and oropharynx, 4 tumors in the nasopharynx and 51 tumors in the cervical region. Ameri et al. did not reported details of the data regarding the tumor site and treatment modality received by the included patients, reporting only that they were patients with cancer in the head and neck region who received radiotherapy treatment and suffered from xerostomia.

Andersson et al., 1995, reported that 12 of their 20 participants were smokers and Kae et al, 2020, reported that 70 of their 109 participants were smokers. The others research did not report details about smokers.

Figure 1 – Prisma 2020 flow diagram

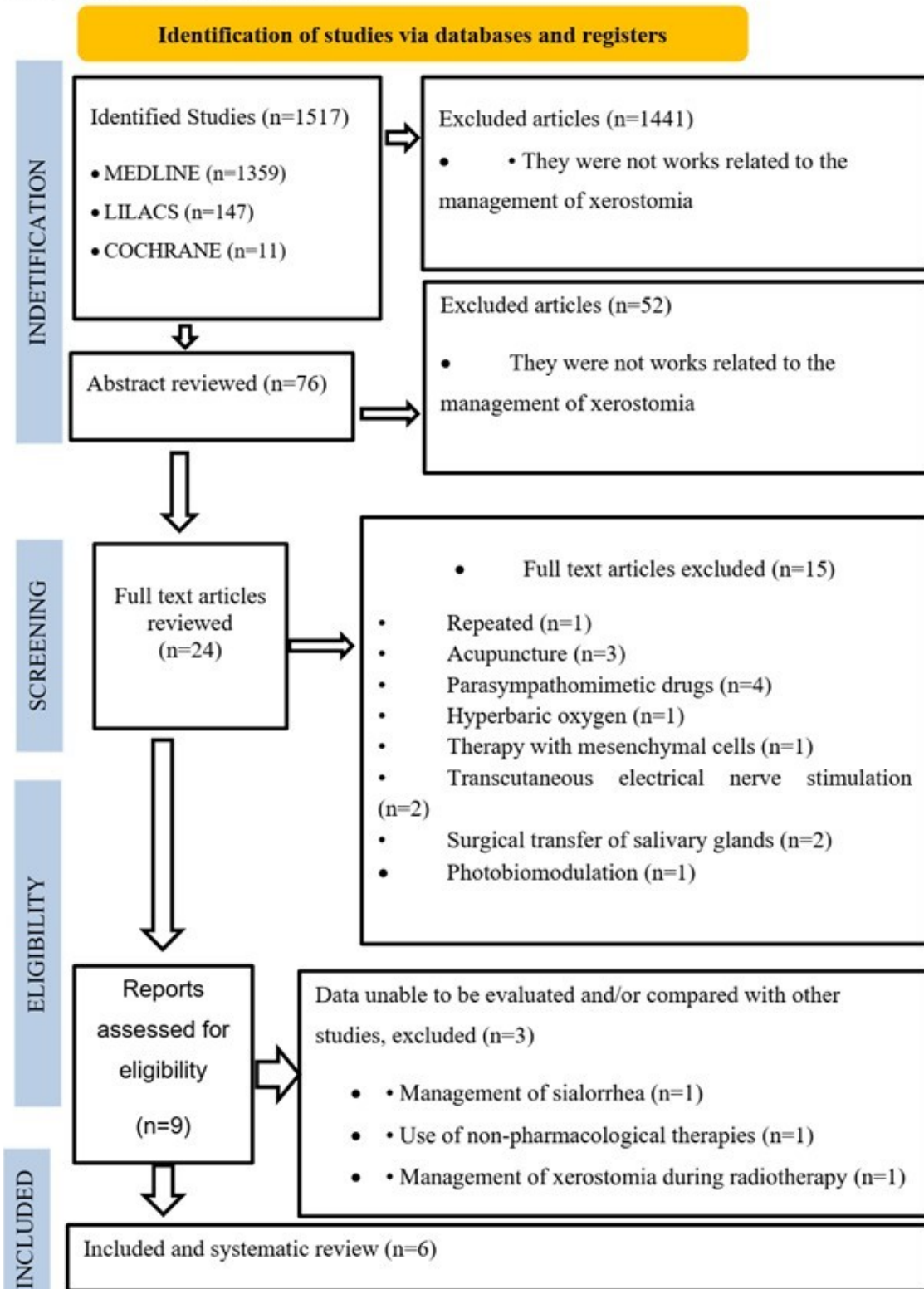


Table 1 – Characteristic of studies included in the systematic review. (n =6)

Authors/ year / participant	Method/ Intervention	Outcomes	Comments
1. Kaae et al., 2020 (N=91)	Daily chewing gum (N=55) X Standard care (N=36)	Reduction of dry mouth was significantly higher for chewing gum ($p=0.05$). A reduction in dry mouth scores was observed for xerostomia assessed by EORTC QLQ-H&N35 for both arms. Salivary flow increased and viscosity decreased upon five minutes of stimulation within both arms ($p<0.001$, respectively), however not significantly difference was observed between arms.	Variables: The Danish validated EORTC QLQ-H&N35 and GRIX questionnaire, unstimulated whole saliva (UWS) and stimulated whole saliva (SWS), viscosity was tested with the Inclined Plane Test (IPT) on a vertical glass plate
2. Ameri et al., 2015 (N=62)	Boiss (experimental group) N=42 X Hypozalix (control group) N=33 Patients were instructed to use the products 3x a day for 4 weeks.	The means obtained on the Visual Analogic Scale (VAS) between all tests and times were statistically significant. Although not statistically significant, 10 people dropped out in the experimental group and 3 in the control group due to complications such as nausea, vomiting, epigastric pain or believing that the therapy was not effective.	Variables: assessments at 2 and 4 weeks after therapy use, physical examination, VAS scale scored from 0 to 10 where 0 was no signs of dry mouth and 10 was severe signs of dry mouth.
3. Momm et al., 2005 (N=120 + 3)	Aldiamed, Glandosane® Carmellose, rapeseed oil spray and Saliva medac spray. They used the 4 products for 1 week each. Three patients withdrew from the study: one patient died of tumor reasons, two patients were non-adherent, thus three more patients were recruited.	All compounds significantly improved xerostomia when compared to baseline ($p < 0.0001$) after one week of therapy use. The gel was rated the best, the carmellose spray was rated the worst by patients, but the compounds alone did not differ significantly in their effects.	There was no washout period. The assessment instruments were an acceptability and xerostomia questionnaire.
4. Jellema et al., 2001 (N=30)	Xialine® X Placebo Randomized, double-blind, 1-week washout, 1-week cross-over	Dry mouth generally decreased with Xialine® and placebo to almost the same degree. A trend was observed for Xialine® to improve speech and sensory problems. Adverse effects: 1 patient was excluded from the study due to nausea in the first week.	The author does not make it clear which product the dropout patient used. To assess the symptoms of xerostomia, the EORTC QLQ-H&N35 questionnaire was used.
5. Senahayake; Piggott and Hamilton-Miller, 1998 (N=10)	Salix STT (Saliva-stimulating Lozenges) take for 7 days was felt necessary.	Nine of the 10 patients completed the 7-day course. The only adverse event was sore tongue. All patients experienced an improvement in dryness of mouth and their quality of life.	Variables: patients self-assessed the dryness of their mouth and its effect on them; Clinical Record Form;
6. Andersson et al., 1995 ¹ (N=20)	Salinum® X MAS-84 Use for 3 weeks, 1 week washout + cross over and use the other product for 3 weeks, Weekly Reviews	General dry mouth symptoms were reduced during periods of use of both products More pronounced improvement in chewing/swallowing ($P<0.001$). taste ($P<0.001$), speech disorders ($P<0.001$), gingival conditions ($P<0.001$) in the Salinum® group	Variables: SWS, VAS scale, acceptability and symptoms questionnaire, periodontal index and gingival bleeding, plaque index, palate material collection for microbiological analysis.



DISCUSSION

Most of the works found during the research phase elucidate local therapies with synthetic compounds or even the use of systemic therapies. The authors also clarify that many of them can trigger some undesirable side effects, which can greatly compromise treatment adherence and even the quality of life of these patients (FURNESS et al., 2011; RILEY et al., 2017).

Patients who undergo cancer treatment have their quality of life compromised due to the chronic effects that the therapy can generate. Xerostomia in this specific population can be relieved over the years, however, in general, the effects are definitive and salivary hypofunction remains, which explains the maintenance of reduced flow in most of the studies reviewed (GE et al., 2020; OBA et al., 2020). For this reason, it is important to focus efforts on improving quality of life and reducing symptoms (JENSEN et al., 2010).

Some studies that included other products of natural composition conducted in groups with xerostomia induced by other factors such as Sjogren's syndrome, polypharmacy and acute reactions to radiotherapy indicate the efficiency of preparations based on natural compounds, a common practice in the East with some well-conducted studies in oncological groups compared with control group and placebos (AITKEN-SAAVEDRA, et al., 2020; LEE et al., 2021). However, due to the diversity of these compounds also the variety of studies, it is difficult to conduct meta-analysis studies, so it is necessary to carry out more research in this field, encouraging the use of a single product in order to improve the factor comparison (MERCADANTE et al., 2021).

There are also lines of research in other fields of medicine that seek to clarify the effectiveness of other therapies based on products of natural composition with different purposes, including neurological disorders such as stress, anxiety and depression, muscle disorders, pain, weakness, fatigue, promotion of analgesia antioxidant, anti-inflammatory action and combating infectious processes (HUANG et al., 2018; HUNG, PERRY & ERNST, 2011; MARTIN & ERNST, 2004).

The care guidelines for patients with xerostomia suggest that there is an adequate level of evidence for the effectiveness of topical products for symptom relief. However, few controlled clinical trials made it difficult to identify products with an alternative composition for the treatment of radioinduced xerostomia (ADA, 2021; ANDERSSON et al., 1995; RILEY et al., 2017).

Several alternative components have been used in the treatment of xerostomia alone or concomitantly and apparently, there is a positive impact on the control



of xerostomia, thus improving the quality of life (NIK-NABIL et al., 2017; PAGLIONI et al., 2020). Considering that quality of life suffers a great negative impact after cancer treatment, it is important to seek measures to improve it (LEE et al., 2021; PAREEK et al., 2016)

AUTHOR'S CONSIDERATIONS

Based on the reviewed studies, we believed that a product with an alternative composition seems to be a good alternative for symptom control in patients with xerostomia, mainly aiming to reduce side effects.

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