Efficacy and safety of oral sprays used to manage dry mouth – Systematic review and network meta-analysis

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Short title: Meta-analysis: Oral sprays for dry mouth

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Abstract

Various substances have been proposed for use as sprays to alleviate dry mouth symptoms. This systematic review with network meta-analysis aimed to assess their efficacy and safety. Six publication databases were searched, along with three protocol registers and two theses and dissertations libraries. Parallel-groups randomized controlled trials involving spray-based interventions to treat dry mouth symptoms were included. Following duplicate study selection and data extraction, data of xerostomia, stimulated and unstimulated salivary flow, adverse effects, and oral health-related quality of life were analyzed. Whenever possible, paired and network meta-analysis were applied using a random-effects model. The risk of bias was assessed using RoB 2, and the certainty of evidence was assessed using GRADE. Fourteen studies (n = 761) addressed 10 spray-based interventions for dry mouth. Findings from paired and network meta-analyses suggest that 1% malic acid is the most effective over-the-counter spray-based intervention for improving xerostomia, as well as stimulated and unstimulated salivary flow. The certainty of evidence to recommend malic acid was low, due to risk of bias, imprecision, and network intransitivity. Besides, safety issues regarding 1% malic acid spray require further evidence. Low-certainty evidence suggests that 1% malic acid spray improves dry mouth better than other over-the-counter spray-based interventions. Most available interventions lack robust evidence to support clinical recommendation.

Keywords: Oral spray; xerostomia; hyposalivation; systematic review; network meta-analysis

INTRODUCTION

Xerostomia is the subjective sensation of dry mouth, which may or may not be linked to hyposalivation – a reduction in salivary flow. More common in older people, it may result from salivary gland dysfunction caused by medication side effects, Sjögren's syndrome, dehydration, gland trauma or tumors, endocrine disorders, or radiation-induced damage, among other factors (1).

This condition affects an estimated 22% of the population, with higher prevalence among the elderly, women, individuals with depressive symptoms, and those on continuous medication (2,3). Reduced salivary flow impairs key oral functions, as saliva aids in food bolus formation, taste, mucosal lubrication, swallowing, speech, acid neutralization, and defense against microorganisms (4). Consequently, it can cause social embarrassment and significantly impair the quality of life of affected individuals (5).

Treatment options for xerostomia and hyposalivation can be categorized into three main types: pharmacological, non-pharmacological, and topical (6). These approaches aid in symptom relief, stimulation of salivary flow, or regeneration of secretory gland tissue (7). The choice of approach depends on the underlying etiology of dry mouth. Pharmacological strategies typically involve systemic drugs with parasympathomimetic, cholinergic, and muscarinic effects, such as pilocarpine, cevimeline, bethanechol, and physostigmine, which aim to increase salivary flow and partially regenerate glandular function (8,9). However, these drugs may cause adverse effects including nausea, bronchoconstriction, bradycardia, and hypotension, and therefore require cautious prescription (10).

Therefore, topic treatments may be an option. They act either by directly lubricating the mouth or by stimulating saliva production through sialagogue effects (6). They can be applied via lozenges, sprays, mouthwashes, gels, oils, chewing gums, and toothpastes (11). Sprays typically replace natural saliva but may also deliver sialagogue substances, such as acids that promote salivation (11).

The use of topical dry-mouth interventions is associated with the severity of oral dryness and with the specific intra-oral location (12). Additionally, specific mechanisms of mouth dryness relief may be related to the better performance of topical substances compared to others. Yet, to our knowledge, no multiple comparisons of different substances applied topically as sprays to relieve dry mouth symptoms have been

attempted. Therefore, this systematic review assessed the dry mouth relief efficacy and safety of oral sprays used to treat mouth dryness.

MATERIALS AND METHODS

This systematic review was designed to answer the question 'How effective and safe are oral sprays used to manage dry mouth?' In this context, dry mouth encompasses both the subjective sensation of dry mouth (xerostomia) and the objective reduction in salivary flow (hyposalivation). The protocol was registered in PROSPERO under registration no. CRD42024563253. The study's PICOS acronym was:

P – People undergoing xerostomia and/or hyposalivation, regardless of the etiology;

I – Oral sprays applied exclusively to treat xerostomia/hyposalivation;

C – Oral sprays applied exclusively to treat xerostomia/hyposalivation;

O – Xerostomia, hyposalivation and oral health-related quality of life;

S – Randomized controlled clinical trials.

1. Search strategy and eligibility criteria

The primary studies were searched in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE through Elsevier, Web of Science (WoS), Scopus, and Latin American and Caribbean Literature in Health Sciences (LILACS) via the Virtual Health Library (VHL). They were also searched in protocol databases, namely the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO), ClinicalTrials.gov, and Brazilian Clinical Trials Registry (ReBEC). Gray literature, considered theses and dissertations, was searched in the Brazilian Digital Library of Theses and Dissertations (BDTD) and the Network Digital Library of Theses and Dissertations (NDLTD). Additionally, manual searches were conducted in the reference lists of included studies and other relevant literature reviews. There were no restrictions on language or publication date. The search strategy was developed by a librarian in PubMed (Table 1) using MeSH terms, free terms, and Boolean operators, and then adapted for use in other databases (Table S1). A sensitive

search strategy was prioritized; therefore, Comparison and Results elements were not included. The last search for studies was conducted on July 15th, 2025.

Adults with xerostomia, hyposalivation, or both, despite their cause, were included. The interventions included oral sprays used exclusively to treat xerostomia/hyposalivation. Comparisons could include placebo sprays, or any other substance applied in the form of oral spray. Primary outcomes included xerostomia, stimulated/unstimulated salivary flow rates and adverse effects. Secondary outcomes involved quality of life related to oral health. The study design included parallel group randomized clinical trials. Summaries or incomplete studies were excluded due to lack of methodological detail.

2. Study selection

The datasets of records were uploaded to Rayyan QCRI where the records were deduplicated. A two-fold selection process was conducted: first, by titles and abstracts, and then, by full-text reading. Both were conducted independently by two blind researchers (LST and JR). To properly select the studies, they were trained in the eligibility criteria and selected a subset containing the first 100 studies. When inconsistencies arose during either the training or selection process, consensus was achieved through discussions involving a third reviewer (SARJ).

3. Extracting and charting of data

Training for data extraction involved extracting information of interest to a previously tested standard form from a subset of included studies. The same researchers involved in study selection (LST and JR) extracted data independently and in a blind manner. Inconsistencies in data extraction were discussed and solved by consensus. Information about the primary studies included authorship, publication year, journal, trial design, number of centers involved, study duration, trial registry number (if any), inclusion/exclusion criteria for participants, number of participants randomized and assessed, age, sex, condition manifested (whether xerostomia, hyposalivation of both), the cause of the condition, interventions (active ingredient involved, concentration, dose, daily frequency of application and duration of treatment), follow-up, outcomes, funding and declaration of conflict of interest.

Data presented in graphs were extracted using GetData Graph Digitizer. When necessary, the change-from-baseline standard deviation was calculated based on sensitivity analyses adopting correlation coefficients 0, 0.5 and 0.9 (14) (Figures S2, S3, S4 and S6).

4. Summarizing and reporting of results

The results were summarized descriptively, referring to the items of the PICOS structure. Additionally, data described by the median, or those adopting non-parametric tests in the primary study, were considered skewed and were presented descriptively.

Pairwise and network meta-analyses were carried out considering the active substance in each spray as an intervention. Pairwise meta-analysis assumed a random effects model, and the mean difference (MD) as effect measure along with the 95% confidence interval (95%CI). Heterogeneity was assessed by the analysis of overlapping 95% confidence intervals and the I^2 statistics. Packages *meta* and *metafor* for R were used for the conventional, pairwise meta-analysis.

The network meta-analysis was conducted using a random-effects Bayesian mixed treatment comparison (MCT) model, combining the different sprays. The choice of the random-effects model was guided by the lower Deviance Information Criterion (DIC) compared to the fixed-effects model. Network geometry was presented graphically and included the number of studies and participants addressing each comparison. When the network did not connect treatments (ex. A vs B and C vs D), we opted to conduct pairwise meta-analysis only. A sampling simulation using the Monte Carlo Markov Chain (MCMC) method was conducted with the following parameters: n.chain = 4, n.iter = 20000, n.adapt = 2000, and thin = 50. The convergence of the model was verified with the Gelman-Rubin test (values lower than 1.05 for the median and for the 97.5% interval). No inconsistency was found in the network, based on the attempt of running a nodesplit test. Also, no multi-arm trial was included. The effect measure of the network meta-analysis was the MD along with the 95% credibility interval (ICr95%). The treatments were ranked based on the positioning probability of each spray, using Litmus Rank-O-Gram and Radial surface under the cumulative ranking curve (SUCRA) graphs. Packages *coda*, *gemtc,* and *rjags* for R (Viena, Austria) were used for the MTC meta-analysis. In

addition, MetaInsight v6.3.0 R-shiny web-based tool was used to provide graphical results.

5 Risk of bias assessment

Risk of bias was assessed using the Cochrane Collaboration's Risk of Bias 2.0 tool for individually randomized parallel group trials. This tool is domain-based and considers five domains to be assessed: bias due to the randomization process, bias due to deviations from intended interventions, bias due to lack of outcome data, bias in outcome measurement, and bias in the selection of reported outcomes. Each domain can be classified as 'high risk', 'low risk' or 'some concerns'. When most domains were compromised by concerns (yellow flag), we rated the risk of bias as high. The graphs of risk of bias assessment were generated using *robvis* web app. Publication bias was not assessed due to the number of studies being smaller than 10.

6 Grading of evidence certainty

The certainty of the evidence was assessed with the GRADE tool.

RESULTS

A total of 163 studies were identified through database and grey literature search (Figure S1). Following deduplication and study selection based on title and abstract, 42 studies were assessed through full-text reading, and 34 were excluded. The reasons for each study exclusion are revealed in Table S2. Information about the fourteen studies included is presented in Table S3.

The study identified 14 parallel-group randomized controlled trials assessing the effect of oxygenated glycerol triester (OGT) spray, electrolyte-containing aqueous solution Salivese spray, mucin-containing Saliva Orthana spray, cold water spray, cold saline spray, Bioxtra spray, ViscoEase spray, 1% malic acid spray, *P. emblica* spray and 10% trehalose spray. Placebos were mostly constituted by water at room temperature, carboxymethyl cellulose solutions or substances similar to the experimental group, yet, without the active ingredient.

1. Xerostomia

Thirteen studies (14-22,24-27) assessed the effect of spray-based interventions on xerostomia. Network meta-analysis for dry mouth was not considered feasible, since interventions applied in similar contexts did not present a common comparison in the network. Therefore, paired meta-analyses were conducted, pooling studies with similar interventions and similar outcome measures.

Three studies (17,18,21) (n = 143) were included in a meta-analysis assessing the effect of 1% malic acid spray on xerostomia based on the Dry Mouth Questionnaire (DMQ). The pooled MD was 1.98 (95%CI = 1.91; 2.06) and the I^2 was 0% (Figure 1.A). Another study (n = 60) addressing the same intervention reported significant alleviation of dry mouth, assessed by Visual Analogue Scale (VAS), at two weeks (24); however, this effect was not significantly different from that of the placebo (MD = -4.6; 95% CI = -10.26 to 1.06). Also, a forth study used the Xerostomia Inventory (XI) to assess dry mouth relief comparing 1% malic acid spray and placebo and observed a significant relief with the intervention group at two weeks (MD = -5.9; 95%CI = -10.37; -1.43) (19).

Two other studies (15,16) (n = 115) compared the effect of OGT oral spray with a commercial saliva substitute (Saliveze®) in xerostomia assessed using a 10-cm visual analogic scale (VAS) that considered values closer to zero as representative of lower dry mouth sensation. The pooled MD was -2.09 (95%CI = -3.76; -0.43) in favor of OGT spray; and the I^2 was 81% (Figure 1.B).

Paterson et al. (22) examined the effectiveness of Visco-ease™ oral spray in treating dry mouth in 43 patients with head and neck cancer undergoing radiotherapy. They verified xerostomia using the Groningen radiotherapy-induced xerostomia (GRIX) questionnaire and found no difference between the active intervention and the placebo at three weeks (MD = 10.4; 95%CI = -2.14; 22.94). Muhamed et al. (24) observed a significant reduction in mouth dryness at 2 weeks using 1% malic acid spray (MD = 0.11; 95%CI = 0.08; 0.13), which did not maintain at 4 weeks (MD = -0.01; 95%CI = -0.04; 0.01). Dry mouth was assessed applying the SXI-D questionnaire. Oztas and Oztas (25) studied the effect of cold water spray and cold saline spray on mouth dryness (measured by 0-10 VAS) in 104 patients who underwent abdominal surgery. Cold water spray significantly reduced mouth dryness compared to the other methods. Piboonratanakit et

al. (26) compared a 10% trehalose oral spray with a carboxymethylcellulose spray to treat xerostomia (measured by 0-10 VAS) for two weeks in 70 head and neck cancer patients who had undergone radiotherapy. They found that both treatments were similarly effective. Another study assessed dry mouth relief promoted by Bioxtra Spray® and placebo at 4 weeks using the Eisbruch grading instrument. The authors found a decrease in Grade 3 (highest grade, meaning dry mouth impacting on diet, sleep, speech, or other activities) and an increase in Grade 1 (dry mouth without interference in habits) in the experimental group. No statistically significant difference was found between the experimental and placebo groups (27).

2. *Stimulated salivary flow*

Four studies (17-20) (n = 216) assessed the effect of 1% malic acid spray on the stimulated salivary flow rate. The pooled MD was 0.19 (95%CI = 0.11; 0.27) and the I^2 was 0% (Figure 2). A fifth study assessed the effect of a salivary substitute with enzymatic system (Bioxtra® spray) on stimulated salivary flow rate of patients irradiated in the head and neck region at 4 weeks. A slight increase in stimulated salivary flow was observed in the experimental group, which was not significantly different from the control group (placebo) (27).

3. *Unstimulated salivary flow*

Seven studies (n = 344) were involved in network meta-analysis (17-19,21,23,24,26). The placebo group was the common comparator of three active treatment sprays, namely 1% malic acid, *P. emblica* and 10% trehalose (Figure S5). Paired and multiple comparison meta-analyses revealed that 1% malic acid spray was favored when compared with placebo. Yet, it did not differ significantly from *P. emblica* and 10% trehalose sprays (Figure 3). Still, the cumulative probability of 1% malic acid being ranked first and second in the multiple comparison was 72% and 25%, respectively (Figure 4).

Another study assessed the effect of a salivary substitute with enzymatic system (Bioxtra® spray) on unstimulated salivary flow rate of patients irradiated in the head and neck region at 4 weeks. No increase in unstimulated salivary flow was observed, either in the experimental or in the control group (27).

4. Adverse effects

Only minor adverse effects were registered by Mouly et al. (15). Nausea was registered in one patient of the Saliveze® group and unpleasant taste was reported in two patients of the Saliveze® group and one patient of the OGT group. Mouly et al. (16) also registered minor adverse events, which included nausea in one patient (Saliveze® group) and unpleasant taste in three patients (one of Saliveze® group and two from the OGT group). Other studies reported that no adverse effects were observed during the study (20,22,24). The remaining studies did not address adverse effects as an outcome.

5. Oral health-related quality of life

Three studies assessed oral health-related quality of life. Niklander et al. (20) used the OHIP-14sp questionnaire and observed significant decrease in OHIP-14sp scores (improvement in oral health-related quality of life) after treatment with 1% malic acid spray, different from the placebo group. Piboonratanakit et al. (26) applied the Xerostomia-related Quality of Life scale (XeQoLs). It consists of 14 questions divided into four dimensions: physical, pain/discomfort, psychological, and social, and employs a 0-10 VAS to assess perceptions of dryness and its impact. Both trehalose and CMC sprays significantly improved xerostomia-related quality of life, reducing difficulties in chewing, swallowing, talking, and taste. Porangaba et al. (27) assessed quality of life using the University of Washington Quality of Life Questionnaire (UW-QOL) following application of Bioxtra® and placebo sprays. The UW-QOL addresses 12 domains, namely pain, appearance, activity, recreation, chewing, swallowing, speech, shoulder, taste, saliva, humor and anxiety and varies from 0 to 100, being the closest to 100 the best level of function. The overall scores increased similarly in both groups. Bioxtra® spray increased scores of pain, chewing, swallowing, speech and saliva, while decreasing the score of taste.

6. Risk of bias

The overall risk of bias was mostly high (Figure S7). The randomization process and outcome measurement were the least compromising domains as to risk of bias, while selection of the reported result and missing outcome data were the most compromising ones.

7. Certainty of evidence

The certainty of evidence was graded for outcomes that allowed pooled numerical results between comparisons. Therefore, it was graded for xerostomia and stimulated salivary flow after application of 1% malic acid spray versus placebo for two weeks (Table 2). Risk of bias and imprecision downgraded the certainty of evidence to low. Besides, the certainty of evidence for the recommendation of OGT over Saliveze® was very low due to risk of bias, inconsistency, and imprecision.

Finally, certainty of evidence of direct, indirect, and network evidence was graded for unstimulated salivary flow at two weeks, having 1% malic acid, 10% trehalose, P. emblica, and placebo sprays as interventions (Table 3). Downgrading occurred due to risk of bias, imprecision and intransitivity (populations were different as to the cause of xerostomia/hyposalivation).

DISCUSSION

This study aimed to assess the efficacy of oral sprays for treating dry mouth through network meta-analysis (NMA), considering each mechanism of action, substance, and/or concentration as a distinct treatment group. However, the NMA was not feasible for most outcomes, primarily due to variations in how measures such as xerostomia and quality of life were reported. Even so, findings from the paired and network meta-analyses suggest that 1% malic acid is the most effective spray among those evaluated for improving xerostomia, as well as unstimulated and stimulated salivary flow. The certainty of evidence to recommend the 1% malic acid spray was low due to risk of bias in primary studies, imprecision, and intransitivity in the network meta-analysis. Additionally, a very low certainty of evidence was found to recommend the OGT spray over Saliveze® artificial saliva substitute.

Ten spray-based interventions were identified in the included studies. Essentially, topically applied substances may act through two distinct mechanisms: saliva substitutes aid in providing a moisture coating to the oral mucosa. This may require frequent spray applications during the day. The second mechanism is based on a sialogogue effect, stimulating the production of saliva by salivary glands (11). Out of the spray-applied

substances, Saliva Orthana, Salivese®, ViscoEase™, cold water, trehalose, and carboxymethyl cellulose solution were based on the first mechanism, while malic acid and *P. emblica* used the second one. The OGT spray attempted to form a lipid layer in the oral mucosa that protects it from mechanical trauma while maintaining moisture, therefore, contributing for the first mechanism (15). Trehalose, a naturally produced sugar by many organisms, provides moisture retention, having also been used in olphthalmology (28). As to the saliva stimulants, both rely on salivary gland stimulation through their acidic content. *P. emblica* is known for its several therapeutic properties along with its acidic content (ascorbic, citric, succinic, ellagic, malic, chebulic and cinnamic acid) (29).

Paired meta-analyses comparing 1% malic acid spray with placebo favored the intervention for both xerostomia and stimulated salivary flow. The network meta-analysis further confirmed its efficacy in improving unstimulated salivary flow, even compared with other active treatments, consistent with previous reviews (30,31). Our findings also corroborate those of See et al. (30), who reported low certainty of evidence supporting the use of malic acid spray.

For xerostomia, only one of the three studies showed a low risk of bias, with concerns related to deviations from the intended interventions, outcome measurement, and selective reporting. Stimulated salivary flow outcomes relied on two of four studies with low risk of bias, whereas unstimulated flow was mainly informed by high-risk studies. Although individual domains rarely indicated high risk, the accumulation of concerns across multiple domains resulted in an overall high-risk classification, limiting the strength of conclusions (32).

The superiority of OGT over aqueous electrolyte spray in relieving dry mouth had already been reported by Furness et al. (11), based on the same primary studies (15,16). The very low certainty of evidence arose from risks of bias (lack of concealed allocation and incomplete reporting), high heterogeneity, and imprecision. Other interventions were supported only by anecdotal evidence, highlighting the need for further studies before recommendations can be made.

It is widely recognized that dry mouth and hyposalivation are more prevalent in older adults (2,3), although their causes may vary. In the included studies, xerostomia was

associated with head and neck radiotherapy to treat cancer, use of psychotropic, antihypertensive, or antidepressant medications, chronic graft-versus-host disease, anesthesia for surgical procedures, and type 2 diabetes. In each case, the intensity, duration, and resolution of symptoms may differ (12). These variations also contributed to intransitivity in the indirect comparisons within the network meta-analysis, as the populations differed by underlying cause of xerostomia, further reducing the certainty of evidence to very low.

Adverse effects were assessed by few studies. Nausea and unpleasant taste were the most common adverse effects found. On the other hand, studies that assessed acidic interventions to stimulate salivary production failed to assess the demineralizing potential of these substances. Saliva is stimulated as an attempt to neutralize acid, which may result in decreased pH in the oral cavity and increase the risk of tooth erosion (31,34). The type of acid and its concentration play a role in erosive potential. Citric acid, for instance, has a highly erosive potential, led by its low pH and by its neutralizable acidity (time required for saliva to neutralize it) (34). Malic acid, on the other hand, is a weaker acid and requires less time to be neutralized by saliva (35). Besides, the combination with fluoride and xylitol has been proven to reduce in 80% the erosive potential of malic acid compared to citric acid (35).

To our knowledge, this is the first study to compare the efficacy of oral sprays for dry mouth using network meta-analysis, taking into account their different mechanisms of action. The study followed a predefined protocol and adhered to Cochrane methods for systematic reviews of interventions, including tools for assessing risk of bias in the included studies. In addition, the certainty of the evidence was evaluated using GRADE criteria to inform potential guideline recommendations.

Amongst the limitations of the study, one can cite the non-retrieval of three studies that could have enhanced the evidence level, the varying instruments and methods for assessment of outcomes that impaired network meta-analysis for outcomes like xerostomia and oral health-related quality of life, the reduced number of trials for each comparison, and the short follow-up (mostly two weeks). Also, some studies disclosed financial conflicts of interest. Finally, some of the studies did not attempt to assess the adverse effects of the interventions.

Spray-based interventions for dry mouth are easy to apply by the patient and usually are associated with minor or no adverse effects. Policy making would benefit from new randomised controlled trials soundly conducted and reported that assess the efficacy of potentially applicable substances, such as malic acid and OGT. Additionally, other substances with the potential to induce topical saliva stimulation or maintain mouth moisture could be identified through a network meta-analysis. Noteworthy, adverse effects must be included in protocols to come, since evidence-based decision-making also relies on this type of effect. More specifically, there is a plausible concern about the medium/long term risk of dental erosion that should be assessed.

CONCLUSION

There is low-certainty evidence suggesting that 1% malic acid spray may improve xerostomia, stimulated and unstimulated salivary flow short term, compared to other oral spray substances. Yet, given the limited level of evidence, policies and guidelines should not recommend it as a universal option. Further well-designed and well-reported studies are needed to strengthen the certainty of evidence for these outcomes and for adverse effects.

Resumo

Diversas substâncias têm sido propostas para uso em sprays para aliviar os sintomas da boca seca. Esta revisão sistemática com metanálise em rede teve como objetivo avaliar sua eficácia e segurança. Foram pesquisadas seis bases de dados de publicações, três registros de protocolos e duas bibliotecas de teses e dissertações. Ensaios clínicos randomizados de grupos paralelos envolvendo intervenções com sprays para tratar os sintomas da boca seca foram incluídos. Após a seleção de estudos duplicados e a extração de dados, foram analisados os dados de xerostomia, fluxo salivar estimulado e não estimulado, efeitos adversos e qualidade de vida relacionada à saúde bucal. Quando possível, foram aplicadas metanálises pareadas e em rede utilizando modelo de efeitos aleatórios. O risco de viés foi avaliado utilizando o RoB 2 e a certeza da evidência foi avaliada utilizando o GRADE. Quatorze estudos (n = 761) abordaram 10 intervenções

com sprays para boca seca. Os resultados das metanálises pareadas e em rede sugerem que o ácido málico a 1% é a intervenção com spray de venda livre mais eficaz para melhorar a xerostomia, bem como o fluxo salivar estimulado e não estimulado. A certeza das evidências para recomendar o ácido málico foi baixa, devido ao risco de viés, imprecisão e intransitividade da rede. Além disso, questões de segurança relacionadas ao spray de ácido málico a 1% requerem mais evidências. Evidências de baixa certeza sugerem que o spray de ácido málico a 1% melhora a xerostomia mais eficazmente do que outras intervenções em spray disponíveis sem receita médica. A maioria das intervenções disponíveis carece de evidências robustas para sustentar a recomendação clínica.

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Table 1. Search strategy built in PubMed

(("Xerostomia"[Mesh] OR Asialia OR Hyposialia OR "Mouth Dryness" OR "Dryness, Mouth" OR "Dry mouth" OR "Mouth, Dry" OR Hyposalivation) AND ("Oral Sprays"[Mesh] OR "Sprays, Oral" OR "Oral Spray" OR "Spray, Oral")) AND ((((((((((randomized controlled trial) OR (randomized controlled trial)) OR (randomized)) OR (placebo)) OR (drug therapy)) OR (randomly)) OR (trial)) OR (groups)) NOT (animals [MeSH] NOT humans [MeSH]))))

Table 2. Certainty of evidence assessment for xerostomia and stimulated salivary flow

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1% malic acid	placebo	Relative (95% CI)	Absolute (95% CI)		
Xerostomia/dry mouth sensation (Comparison: 1% malic acid vs placebo) (follow-up: 2 weeks)												
3	randomised trials	serious[a,b,c]	not serious	not serious	serious[d]	none	74	69	-	MD 1.98 higher (1.91 higher to 2.06 higher)	⨁⨁◯◯ Low[a,b,c,d]	CRITICAL
Stimulated salivary flow (Comparison: 1% malic acid vs placebo) (follow-up: 2 weeks)												
4	randomised trials	serious[a,b,c]	not serious	not serious	serious[d]	none	112	104	-	MD 0.19 higher (0.11 higher to 0.27 higher)	⨁⨁◯◯ Low[a,b,c,d]	IMPORTANT
Xerostomia/dry mouth sensation (Comparison: OGT spray vs Saliveze) (follow-up: 2 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	1% malic acid	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a,e]	serious[f]	not serious	serious[d]	none	59	56	-	MD 2.09 lower (3.76 lower to 0.43 lower)	⨁◯◯◯ Very low[a,d,e,f]	CRITICAL

CI: confidence interval; MD: mean difference

Explanations

a. Bias due to possible deviation from intended intervention

b. Bias due to missing outcome data

c. Bias in selection of the reported result

d. Despite the statistical difference between intervention group and control group, the number of participants was way below 400 (200 per group), as recommended by Guyatt et al. (2011).

e. Concerns related to the full report of the results

f. High heterogeneity detected

Table 3. GRADE rating based on direct, indirect and mixed (network) evidence for unstimulated salivary flow

	Direct evidence		Indirect evidence		Network evidence	
Comparison	Mean difference (95%CI)	Quality of evidence	Mean difference (95%CrI)	Quality of evidence	Mean difference (95%CrI)	Quality of evidence
1% malic acid vs placebo	0.08 (0.06 to 0.10)	⊕⊕◯◯*,§ Low	-	-	0.079 (0.037 to 0.11)	⊕⊕◯◯*,§ Low
P. emblica vs placebo	0.02 (-0.05 to 0.09)	⊕⊕◯◯*,§ Low	-	-	0.021 (-0.081 to 0.12)	⊕⊕◯◯*,§ Low
10% trehalose vs placebo	0.02 (-0.10 to 0.14)	⊕⊕◯◯*,§ Low	-	-	0.021 (-0.12 to 0.15)	⊕⊕◯◯*,§ Low
1% malic acid vs *P. emblica*	-	-	0.056 (-0.10 to 0.11)	⊕◯◯◯*,§,¶ Very low	0.058 (-0.048 to 0.17)	⊕◯◯◯*,§,¶ Very low
1% malic acid vs 10% trealose	-	-	0.057 (-0.70 to 0.74)	⊕◯◯◯*,§,¶ Very low	0.058 (-0.082 to 0.20)	⊕◯◯◯*,§,¶ Very low
P. emblica vs 10% trealose	-	-	0.0003 (-0.17 to 0.17)	⊕◯◯◯*,§,¶ Very low	0.0016 (-0.17 to 0.18)	⊕◯◯◯*,§,¶ Very low

* Limitations (risk of bias); § Imprecision; ¶ Intransitivity.

Figure 1. Pairwise meta-analysis on xerostomia: A. Comparison between 1% malic acid and placebo; B. Comparison between OGT and Saliveze®

Figure 2. Pairwise meta-analysis comparing 1% malic acid with placebo on stimulated salivary flow

Figure 3. A. Pairwise meta-analysis between groups; B-E: Multiple comparison between groups (Mean difference and 95% credible interval): B. Comparison with placebo; C. Comparison with 1% malic acid spray; D. Comparison with *P. emblica* spray; E. Comparison with 10% trehalose spray

Figure 4. A. SUCRA; B. Cumulative ranking probability graph

Figure 1.

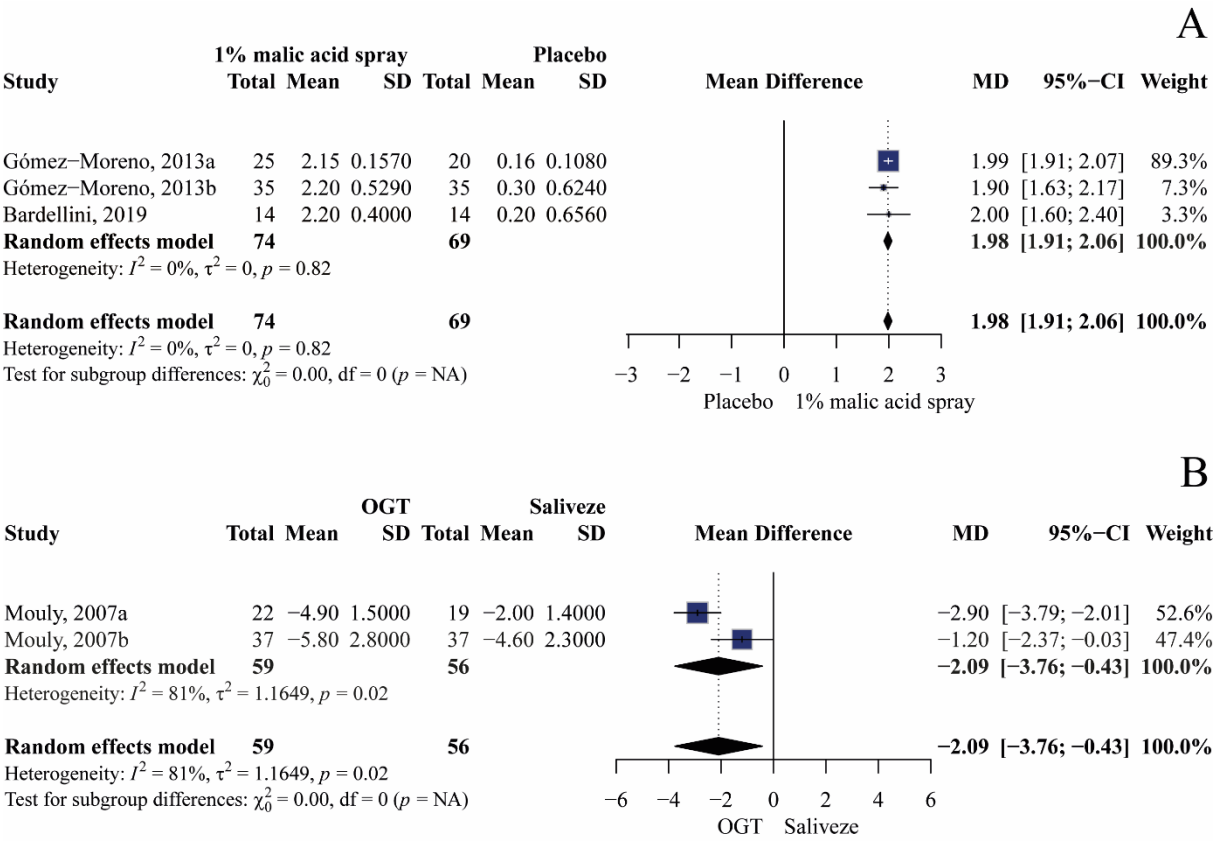


Figure 2.

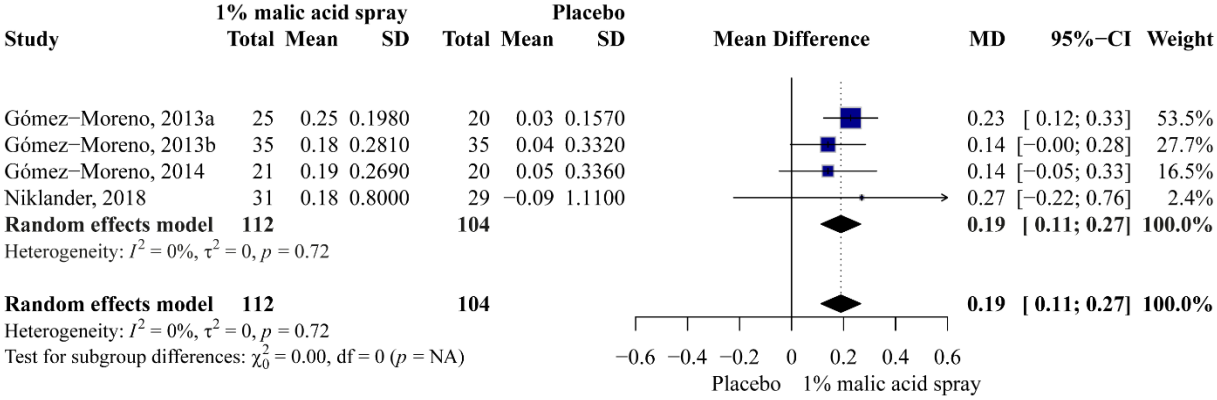


Figure 3.

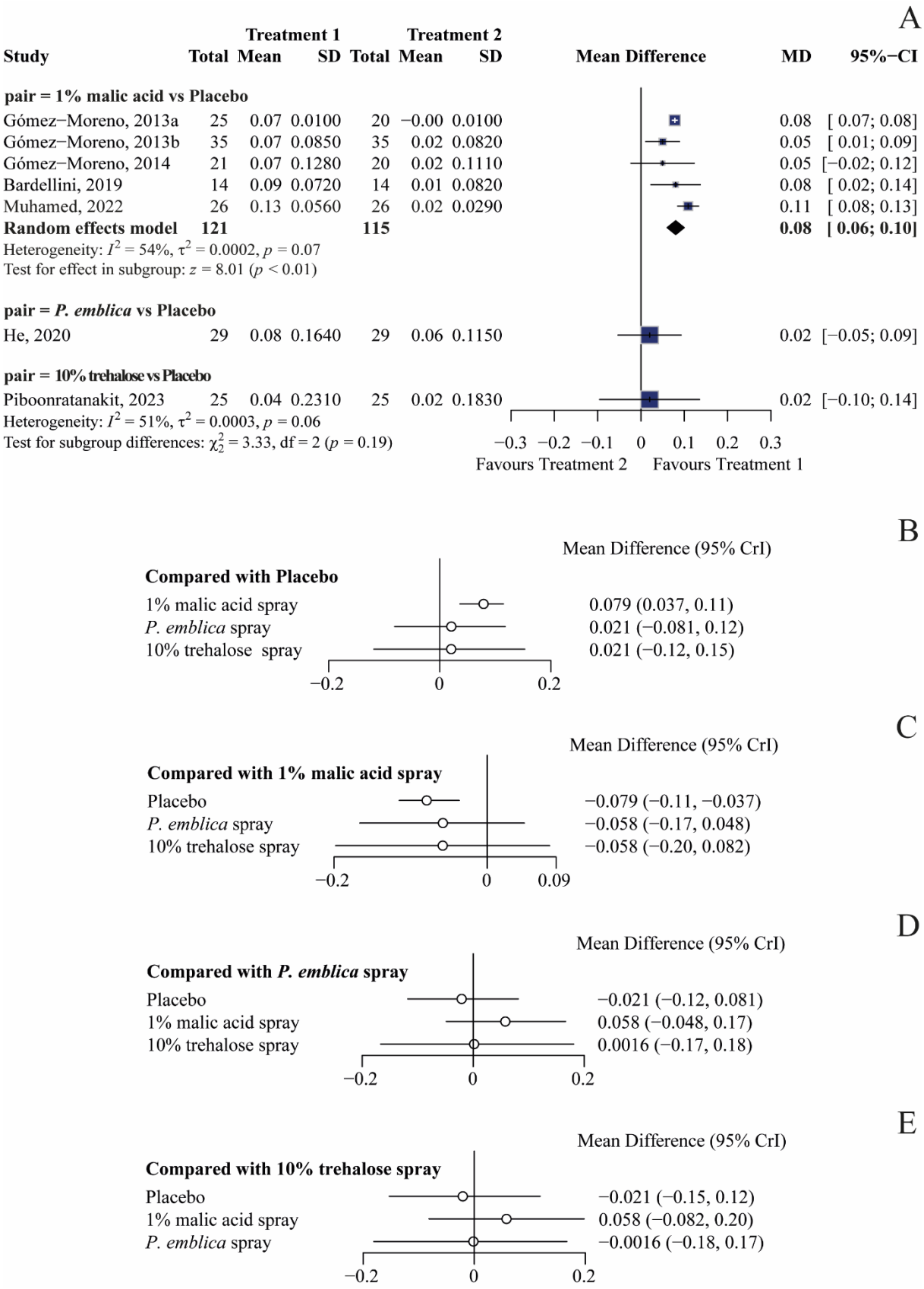
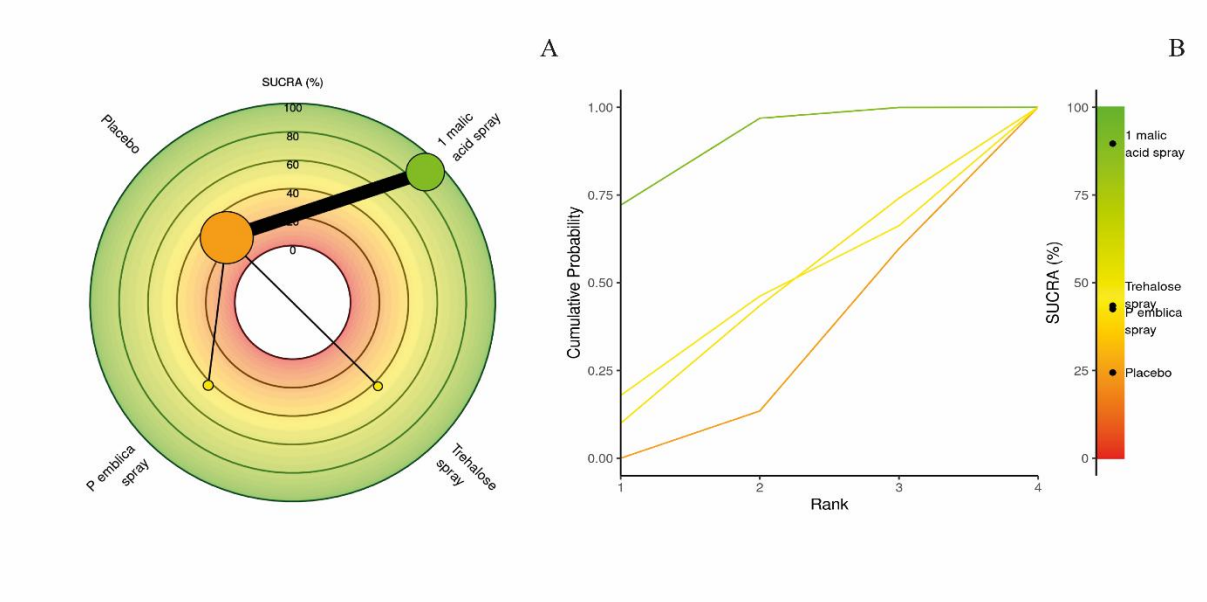


Figure 4.



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