Data Documentation

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

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Brief method description

Data were gathered to answer the question: 'How effective and safe are oral sprays used to manage dry mouth?' The protocol was registered in PROSPERO under registration no. CRD42024563253. 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), International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO), ClinicalTrials.gov, and Brazilian Clinical Trials Registry (ReBEC). Gray literature was searched in the Brazilian Digital Library of Theses and Dissertations (BDTD) and the Network Digital Library of Theses and Dissertations (NDLTD). Studies were included when they involved adults with xerostomia, hyposalivation, or both and oral sprays used exclusively to treat xerostomia/hyposalivation as interventions. 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. The studies were selected by trained researchers independently and blinded, similar to data extraction. Data presented in graphs were extracted using GetData Graph Digitizer. When necessary, the change-from-baseline standard deviation was calculated based on sensitivity analyses testing correlation coefficients 0, 0.5 and 0.9.

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.

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.

Components of the dataset

1. Datasets for paired meta-analysis of xerostomia assessed by the Dry Mouth Questionnaire (DMQ)

Two files entitled ‘pair_xerostomia_dmq’ with extensions .xlsx and .csv containing the dataset for paired meta-analysis of 1% malic acid spray vs. Placebo with three studies included (Gómez-Moreno, 2013a, Gómez-Moreno, 2013b and Bardellini, 2019).

The file is composed by eight columns, as follows:

Author – represents the studies;

t_n – represents the number of participants in the treatment group;

t_media – represents the mean value for xerostomia in the DMQ of the treatment group;

t_dp – represents the standard deviation of xerostomia of the treatment group;

c_n – represents the number of participants in the control group;

c_media – represents the mean value for xerostomia in the DMQ of the control group;

c_dp – represents the standard deviation of xerostomia of the control group;

par – represents the pair being compared (CA), in which C means 1% malic acid spray and A means Placebo

2. Datasets for paired meta-analysis of xerostomia assessed by 10-cm Visual Analogue Scale (VAS)

Two files entitled ‘pair_xerostomia_vas’ with extensions .xlsx and .csv containing the dataset for paired meta-analysis of Saliveze® vs. Oxygenated Glycol Triester (OGT) spray with two studies included (Mouly, 2007a and Mouly, 2007b).

The file is composed by eight columns, as follows:

Author – represents the studies;

t_n – represents the number of participants in the treatment group;

t_media – represents the mean value for xerostomia measured by VAS of the treatment group;

t_dp – represents the standard deviation of xerostomia of the treatment group;

c_n – represents the number of participants in the control group;

c_media – represents the mean value for xerostomia measured by VAS of the control group;

c_dp – represents the standard deviation of xerostomia of the control group;

par – represents the pair being compared (IB), in which I means Saliveze® and B means OGT spray

3. Datasets for paired meta-analysis of Stimulated Salivary Flow (SSF)

Two files entitled 'pair_stimulated_flow' with extensions .xlsx and .csv containing the dataset for paired meta-analysis of 1% malic acid spray vs. Placebo with four studies included (Gómez-Moreno, 2013a, Gómez-Moreno, 2013b, Gómez-Moreno, 2014 and Niklander, 2018).

The file is composed by eight columns, as follows:

Author – represents the studies;

t_n – represents the number of participants in the treatment group;

t_media – represents the mean value of SSF of the treatment group;

t_dp – represents the standard deviation of xerostomia of the treatment group;

c_n – represents the number of participants in the control group;

c_media – represents the mean value of SSF of the control group;

c_dp – represents the standard deviation of xerostomia of the control group;

par – represents the pair being compared (CA), in which C means 1% malic acid spray and A means Placebo

4. Datasets for paired meta-analysis of Unstimulated Salivary Flow (USF)

Two files entitled 'pair_unstimulated_flow' with extensions .xlsx and .csv containing the dataset for paired meta-analysis of 1% malic acid spray vs. Placebo, *Phyllantus emblica* spray vs. Placebo and 10% trehalose spray vs. Placebo. The dataset included seven studies (Gómez-Moreno, 2013a, Gómez-Moreno, 2013b, Gómez-Moreno, 2014, Bardellini, 2019, He, 2020, Muhamed, 2022 and Piboonratanakit, 2023).

The file is composed by eight columns, as follows:

Author – represents the studies;

t_n – represents the number of participants in the treatment group;

t_media – represents the mean value of USF of the treatment group;

t_dp – represents the standard deviation of xerostomia of the treatment group;

c_n – represents the number of participants in the control group;

c_media – represents the mean value of USF of the control group;

c_dp – represents the standard deviation of xerostomia of the control group;

par – represents the pairs being compared: CA, in which C means 1% malic acid spray and A means Placebo, EA, in which E means *P. emblica* spray and A means Placebo and FA, in which F means 10% trehalose spray and A means Placebo.

5. Datasets for Multiple Treatment Comparison (MTC) meta-analysis of Unstimulated Salivary Flow (USF)

Two files entitled 'mtc_unstimulated_flow' with extensions .xlsx and .csv containing the dataset for MTC meta-analysis of Placebo, 1% malic acid spray, *Phyllantus emblica* spray and 10% trehalose spray. The dataset included seven studies (Gómez-Moreno, 2013a, Gómez-Moreno, 2013b, Gómez-Moreno, 2014, Bardellini, 2019, He, 2020, Muhamed, 2022 and Piboonratanakit, 2023).

The file is composed by five columns, as follows:

study – represents the studies;

treatment – represents the treatment groups;

sampleSize – represents the number of participants in the groups;

mean – represents the mean value of USF of the groups;

std.dev – represents the standard deviation of USF

6. Datasets for Multiple Treatment Comparison (MTC) meta-analysis of Unstimulated Salivary Flow (USF)

Two files entitled ‘mtc_unstimulated_flow_metainsight’ with extensions .xlsx and .csv containing the dataset for MTC meta-analysis of Placebo, 1% malic acid spray, *Phyllantus emblica* spray and 10% trehalose spray.

These files were organized to be applied in MetaInsight v6.3.0 R-shiny web-based tool.

The dataset included seven studies (Gómez-Moreno, 2013a, Gómez-Moreno, 2013b, Gómez-Moreno, 2014, Bardellini, 2019, He, 2020, Muhamed, 2022 and Piboonratanakit, 2023).

The file is composed by five columns, as follows:

study – represents the studies;

T – represents the treatment groups;

Mean – represents the mean value of USF of the groups;

SD – represents the standard deviation of USF;

N – represents the number of participants in the groups

7. Datasets of Risk of Bias (RoB) analysis

Two files entitled ‘risk_of_bias’ with extensions .xlsx and .csv containing the dataset for analysis of risk of bias with the Cochrane Risk of Bias (RoB) Tool 2.0. The dataset included seven studies (Sweeney, 1997, Mouly, 2007a, Mouly, 2007b, Gómez-Moreno, 2013a, Gómez-Moreno, 2013b, Gómez-Moreno, 2014, Niklander, 2018, Bardellini, 2019, Paterson, 2019, He, 2020, Muhamed, 2022, Oztas, 2022, Piboonratanakit, 2023,

Porangaba, 2024). Each domain of each study is rated ‘Low’, ‘Some concerns’ or ‘High’ for ‘low risk of bias’, ‘concerns’ and ‘high risk of bias’.

The file is composed by eight columns, as follows:

study – represents the studies;

D1 – represents the domain ‘Bias arising from the randomization process’;

D2 – represents the domain ‘Bias due to deviations from intended interventions’;

D3 – represents the domain ‘Bias due to missing outcome data’;

D4 – represents the domain ‘Bias in measurement of the outcome’;

D5 – represents the domain ‘Bias in selection of the reported result’;

Overall – represents the overall analysis of risk of bias of each study;

Weight – represents the weight of each study

8. Script for paired and Multiple Treatment Comparison (MTC) in RStudio

R file entitled ‘dry_mouth_meta-analyses’ containing the script for paired and MTC meta-analyses used in R 4.5.2 and RStudio Version 2025.09.2+418.

The file contains the script to analyse:

1. Xerostomia measured with Dry Mouth Questionnaire (DMQ)
2. Xerostomia measured with 10 cm Visual Analogue Scale (VAS)
3. Stimulated salivary flow
4. Unstimulated salivary flow

9. Supplementary files

PDF file entitled ‘Supplementary files’ containing supplementary information to the manuscript.

The file contains the following information:

Table S1. Search strategies applied to the databases.

Table S2. Excluded records with reasons.

Figure S1. Study flow diagram.

Table S3. Characteristics of studies, population, interventions and outcomes.

Figure S2. Sensitivity analysis of the r coefficient for SD of the change from baseline for xerostomia assessed by DMQ involving the comparison between 1% malic acid spray and placebo.

Figure S3. Sensitivity analysis of the r coefficient for SD of the change from baseline for xerostomia assessed by 10 cm VAS involving the comparison between OGT spray and Saliveze. A. r = 0; B. r = 0.5; C. r = 0.9.

Figure S4. Sensitivity analysis of the r coefficient for SD of the change from baseline for stimulated salivary flow (SSF) involving the comparison between 1% malic acid spray and placebo. A. r = 0; B. r = 0.5; C. r = 0.9.

Figure S5. Network configuration.

Figure S6. Sensitivity analysis of the r coefficient for SD of the change from baseline for ustimulated salivary flow (USF) involving the comparison between 1% malic acid spray, P. emblica spray, trehalose spray and placebo. A. r = 0; B. r = 0.5; C. r = 0.9.

Figure S7. A. Risk of bias of each individual study; B. Percentage of risk of bias across studies.

Table S4. PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis.