**Interventions for the management of radiotherapy-induced xerostomia and hyposalivation: a systematic review and meta-analysis**

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**ABSTRACT**

**Introduction:** Salivary gland hypofunction is a common and permanent adverse effect of radiotherapy to the head and neck. Randomised trials of available treatment modalities have produced unclear results and offer little reliable guidance for clinicians to inform evidence-based therapy. We have undertaken this systematic review and meta-analysis to estimate the effectiveness of available interventions for radiotherapy-induced xerostomia and hyposalivation.

**Methods:** We searched MEDLINE, Cochrane Central, EMBASE, AMED, and CINAHL database through July 2016 for randomized controlled trials comparing any topical or systemic intervention to active and/or non-active controls for the treatment of radiotherapy-induced xerostomia. The results of clinically and statistically homogenous studies were pooled and meta-analysed.

**Results:** 1732 patients from twenty studies were included in the systematic review. Interventions included systemic or topical pilocarpine, systemic cevimeline, saliva substitutes/mouthcare systems, hyperthermic humidification, acupuncture, acupuncture-like transcutaneous electrical nerve stimulation, low-level laser therapy and herbal medicine. Results from the meta-analyses, which included six studies, suggest that both cevimeline and pilocarpine can reduce xerostomia symptoms and increase salivary flow compared to placebo, although some aspects of the relevant effect size, duration of the benefit, and clinical meaningfulness remain unclear. With regard to interventions not included in the meta-analysis, we found no evidence, or very weak evidence, that they can reduce xerostomia symptoms or increase salivary flow in this population.

**Conclusions:** Pilocarpine and cevimeline should represent the first line of therapy in HNC survivors with radiotherapy-induced xerostomia and hyposalivation. The use of other treatment modalities cannot be supported on the basis of current evidence.

**Keywords: xerostomia, radiotherapy, acupuncture, sialogogue, saliva**

## INTRODUCTION

Head and neck cancer (HNC) is the sixth most common cancer worldwide and is often managed with radiotherapy, either as monotherapy or in association with chemotherapy and surgery [1]. When salivary glands are within the irradiated field, irreversible salivary glands damage occurs in 63-93% of the patients [2]. Salivary gland damage typically manifests as reduced saliva secretion, which in turn can translate into a subjective sensation of dry mouth (xerostomia), oral discomfort, altered taste, difficulty with speaking, swallowing, chewing, and increased risk of dental disease. Overall hyposalivation and related xerostomia can cause a substantial reduction in quality-of-life (QoL) [2].

A wide range of interventions for salivary gland hypofunction is available [3]. Stimulation of salivary gland function may be appropriate for patients with some degree of residual salivary gland parenchyma, and it can be attempted through sialogogue medications (such as pilocarpine and cevimeline) [4], or activating the salivary reflex arch via chewing gums or sucking pastilles and lozanges [5]. Topical application of salivary substitutes can offer some benefit by providing a moisture-retaining coating onto the oral mucosa [6]. Other interventions, such as acupuncture, have also been used to increase saliva production, possibly by enhancing peripheral blood flow [7]. However there is currently little robust evidence to inform the management of hyposalivation and xerostomia in this population. Some of the available systematic reviews have not specifically focused on HNC patients but rather considered individuals with xerostomia due to a variety of causes [5]. Others focussed on single intervention [8-11], or presented a number of methodological weaknesses [12-14]. We have undertaken this multiple-treatment systematic review and meta-analysis in order to help estimate the effectiveness of available treatments and contribute to develop evidence-based guidelines for the management of radiotherapy-induced hyposalivation and xerostomia.

## METHODS

We developed a protocol that defined inclusion criteria, search strategy and outcomes of interest. The reporting of this systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15]. For the identification of studies to be included in this review, we developed detailed search strategies for each database (Medline, Embase, The Cochrane Central Register of Controlled Trials, Cinahl, Amed). We searched reference lists of retrieved reports for additional references. The last literature search was performed on the 07$^{th}$ of July 2016. Study inclusion criteria were (i) design: randomized controlled trials; (ii) population: adults with a diagnosis of radiotherapy-induced xerostomia; (iii) intervention: techniques designed to stimulate saliva production or to replace saliva; (iv) control group: placebo, no intervention, another active intervention or a combination of the aforementioned options. The interventions could be given by any route, formulation, or dose. No language restrictions were imposed. Citations were screened by two independent reviewers and full reports of potentially relevant studies were obtained. The methodological quality assessment of the selected trials was performed according to the Cochrane Collaboration tool for assessing risk of bias [16].

The primary subjective outcome measure of this review was the mean overall change in xerostomia symptoms, which was assessed by change in a visual analogue scale (VAS). Secondary objective outcomes were changes in QoL and salivary flow. We looked in detail at the time endpoints used for collection of the outcome measures; in particular we considered whether measurements at endpoint were taken shortly after the intervention (e.g. few minutes or hours) or away from treatment completion (therefore representing xerostomia symptoms and salivary flow during resting condition). Further, we considered incidence of adverse effects and proportion of patients dropping out as indicators of safety and acceptability.

We summarized the effect size for continuous data using the mean difference (MD) with 95% confidence intervals (95% CI). For categorical data, we calculated odd ratio (OR) of improvement, with 95% CI. Heterogeneity between trials was investigated using the $I^2$ index. A fixed effect model was used unless statistical heterogeneity was significant ($p<0{\cdot}05$), after which a random effect model was used.

## RESULTS

Figure 1 shows the process of study selection, leading to the inclusion of 20 studies in the systematic review, with a total of 1732 patients. Table 1 shows summary of trial characteristics. Table 2 shows study populations, interventions, and extracted outcome measures for eligible trials. Seventeen studies used changes in xerostomia symptoms as an outcome; outcome measures included the visual analogue scale (nine studies) [17-25], the xerostomia inventory (one study) [26], the Walizer Mouth Dryness questionnaire (one study) [27], the global rating of change scale (two studies in one paper) [28], general xerostomia questionnaires (two studies) [29, 30], and the xerostomia items of the European Organization for Research and Treatment of Cancer Quality of Life Head and Neck Module (EORTC-H&N35) instrument (two studies) [31, 32]. At endpoint, symptoms were assessed shortly after administration of the intervention in three studies [28, 29], and after 180 minutes in one trial [19], and therefore refer to symptoms perceived by participants during enhancement of salivary gland function. Two studies collected xerostomia symptom measurements one or more weeks after completion of the experimental treatment [31, 33], therefore referring to symptoms perceived by patients during resting salivary condition. Timing of measurement collection at endpoint was unclear in twelve studies [17, 18, 20-23, 25-27, 30, 32, 34].

Twelve trials used changes in salivary function assessed through unstimulated sialometry as an outcome [17-19, 21, 23, 25, 26, 28, 29, 31, 33, 35]. At endpoint, salivary function was assessed shortly after the intervention in four studies [28, 29, 35], after 60 minutes in two studies [17, 18], and after 180 minutes in one study [19]. Two studies assessed salivary flow one or more weeks after completion of the experimental treatment [31, 33] whereas the timing of salivary flow collection at endpoint remained unclear in three studies [21, 23, 25].

Five studies used changes in QoL scores using five different outcome measures including the Oral Health Impact Profile [OHIP-49] and University of Washington

Quality of Life Questionnaire [UW-QoL] questionnaire in one study [34], and the General Oral Health Assessment Index [GOHAI] [26], the EORTC-H&N35 [31], the Xerostomia-Related Quality of Life Scale [XeQoL] [33], and the short version of the Oral Health Impact Profile [OHIP-14] [23]. Two studies collected QoL measures one or more weeks after completion of the intervention [31, 33], whereas timing of outcome collection was unclear in three studies [26, 29, 34].

**Risk of bias**

We considered nine studies (45%) to have a low overall risk of bias (Figure 2). Adequate sequence generation and concealment was reported in 75% and 65% of studies respectively. Blinding of participants to the allocated treatment by use of a placebo was done in 11 of the included studies (55%). Outcome assessors were blinded to allocated treatment in 13 trials (65%). Over 90% of the included studies reported complete outcome data without selective reporting.

**Systematic Review**

***Systemic pilocarpine vs placebo.***

Two placebo-controlled trials with low risk of bias reported a reduction in xerostomia symptoms after 12-week therapy with systemic pilocarpine [17, 18]. The studies also reported a short-term (measured at 60 min) increase in salivation associated with use of a single tablet of pilocarpine. The magnitude of improvement was however unclear as both studies only reported the number of patients who had an arbitrary reduction of at least 25mm in the VAS or any increases in salivation. Clinical significance remains unknown. Adverse side effects (sweating, urinary frequency and nausea) were seen more frequently in individuals using pilocarpine than in the placebo group, with 15-29% of patients in the pilocarpine group withdrawing from the study.

***Systemic cevimeline vs placebo.***

Two research groups assessed the effectiveness of oral cevimeline in three studies with low risk of bias [28, 34]. One showed a clinically meaningful improvement in dry mouth symptoms in the intervention group, however the magnitude of improvement was unclear. The second study failed to show any significant difference between the active group and placebo. Both studies reported that 12-week of cevimeline therapy is associated with a significant, albeit small, increase in salivation, of possible clinical significance. Adverse side effects (sweating and dyspepsia) were seen more frequently in individuals using cevimeline, with 13-14% of individuals in the cevimeline group withdrawing from the study. A second research group assessed the effects of six weeks of cevimeline therapy upon QoL in a study with unclear risk of bias due to unclear reporting on allocation concealment; they observed no significant differences between experimental and placebo groups [34].

***Systemic pilocarpine vs "topical" pilocarpine vs topical placebo.***

The topical administration of pilocarpine has been attempted in order to minimize absorption and related adverse side effects. Taweechaisupapong et al reported a cross-over trial, which they claim was double blinded, where patients received every ten days one single pilocarpine tablet to be swallowed, or one pilocarpine lozenge (3 mg or 5 mg dose) or one placebo lozenge both to be dissolved in the mouth [19]. The study reported that the use of one 5mg lozenge was associated with a short-term (measured at 180 minutes) reduction in xerostomia and increase in salivary flow in significantly more patients than the 3mg lozenge, 5mg pilocarpine tablet and placebo. However, the magnitude of improvement was unclear and clinical significance unknown. No adverse effects were reported. This study was considered at high risk of bias of blinding participants and personnel because, although the authors stated it was a double-blind study, the investigators and the patients knew if they were receiving the lozenge (to be dissolved) or the tablet (to be swallowed). Also, it is rather questionable that dissolving pilocarpine lozenges without spitting the content out represents topical treatment.

***Saliva substitutes vs "topical" pilocarpine.***

One cross-over trial at high risk of bias because of its unblinded design studied the effect of three-month use of a spray containing mucin-based artificial saliva (Saliva Orthana) compared to a mouthwash containing pilocarpine [20]. The study failed to demonstrate statistically significant differences in xerostomia symptom between the two groups. Also, it is rather questionable that this was a topical intervention as participants were allowed to swallow the medication.

***Mouthcare system vs other mouthcare system.***

Three trials evaluated the effects of "mouthcare systems" containing a combination of artificial saliva gel, and/or oral rinse, and/or spray, and/or toothpaste [21, 22, 25]. Epstein reported in a high-quality cross-over trial at low risk of bias that patients using Biotene gel and toothpaste (enzyme-based and hydroxyethylcellulose-based artificial saliva) for two weeks had significantly reduced xerostomia symptom on waking (VAS) and increased stimulated salivary flow compared to controls using carboxymethylcellulose gel and commercial toothpaste, when data were analysed for carryover effect. However the magnitude of the effect and clinical meaningfulness was unclear [25]. The same study design was used by Nagy et al who obtained similar results [21]. However, the latter study should be considered at high risk of bias as, although study measurements refer to the post-radiotherapy period, the experimental intervention and placebo treatment were commenced during radiotherapy. Shahdad et al studied the effects of two weeks of therapy with two enzyme-based salivary substitutes, Oral Balance or BioXtra mouthcare systems (gel, mouthwash and toothpaste) in a double-blind cross-over study at low risk of bias [22]. Participants using BioXtra treatment, which has higher viscosity and contains additional salivary peptides and proteins, achieved a greater improvement in xerostomia symptoms compared to those using Oral Balance mouth care system. Clinical meaningfulness of the reported improvement is unknown.

***Salivary substitutes vs other salivary substitutes or placebo.***

Three cross-over trials compared salivary substitutes vs other salivary substitutes or placebo [26, 30, 32]. McMillan investigated a novel intra-oral device for the slow release of Oral Balance gel versus an oral bolus of the same gel in a four-week randomised cross-over study, which did not show any significantly different effect upon xerostomia symptoms (Xerostomia Inventory) or salivary flow [26]. However, changes in oral health-related quality of life scores (GOHAI) were higher in participants using the device. We considered this study as being at high risk of bias because of its single-blind design.

Jellema studied the effects of one-week use of a xanthan gum-based salivary substitute (Xialine) versus placebo and found no significant difference upon xerostomia symptoms (xerostomia questions of QLQ-H&N35) [32]. Momm tested the effects of one-week use of four different salivary substitutes and reported a significant reduction in xerostomia symptoms with respect to baseline for all groups but not difference among the four groups [30]. We considered the studies of Jellema and Momm to be at high risk of bias due to the lack of information on blinding of participants and investigators.

***Acupuncture vs sham acupuncture or educational oral care sessions.***

Three controlled trials investigated the therapeutic efficacy of acupuncture in radiation-induced xerostomia [29, 31, 35]. The single-blinded study of Cho et al reported no statistically significant difference in salivary flow or xerostomia in the active group (real acupuncture) versus controls (sham acupuncture) after six weeks of twice-a-week treatment [29]. Simcock et al studied the effects of eight weeks of once–a-week acupuncture versus educational oral care session (including advice on the use of artificial saliva) and reported that those having acupuncture were more likely to report an improvement in xerostomia symptoms (as per QLQ-H&N35 and other dry mouth questions) compared to controls [31]. Magnitude of the effect, as well as clinical significance, was unclear. There were no differences with respect to salivary flow or QoL. Finally Blom did not observed any statistical difference in

salivary flow between participants randomised to twelve weeks of real or superficial acupuncture [35]. We deemed the three studies to have high risk of bias due to the overall poor reporting of randomisation and blinding.

***Hyperthermic, supersaturated humidification vs standard bedside humidifier*.**

One cross-over study assessed the effectiveness of two-week use of a device delivering hyperthermic, supersaturated humidification through a nasal cannula compared to a standard bedside humidifier [27]. Dry mouth questionnaires and the visual analogue score showed no significant differences between the two devices in lessening xerostomia symptoms. This study was considered at unclear risk of bias due to unclear sequence generation, allocation concealment, and blinding.

***Acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) vs pilocarpine.***

One unblinded study investigated the effects of twelve weeks of acupuncture-like transcutaneous electrical nerve stimulation (twice-weekly for a total of 24 sessions of 20 minutes each) versus pilocarpine [33], and found no significant difference in Xerostomia-related Quality of Life Scale score or salivary flow between the groups. This study was considered at high risk of bias because of lack of details regarding sequence generation, allocation concealment and blinding.

***Low-level laser therapy vs sham low-level laser therapy.***

One trial tested the effectiveness of low-level laser therapy in improving xerostomia symptoms (VAS), salivary flow and quality of life (assessed through the Oral Health Impact Profile questionnaire) [23]. The groups underwent two weekly sessions of low-level laser therapy for six weeks but in the control group a plastic tip blocked the emission of radiation. The study failed to show any significant difference between the groups with regards to long-term changes in xerostomia, salivary flow or QoL score. This study was considered at unclear risk of bias due to unclear sequence generation, allocation concealment and blinding.

***Herbal compound vs salivary substitute***

One open-label parallel study assessed the effectiveness of four-week use of an herbal compound containing Malva sylvestris and Alcea digitata powder compared to artificial saliva (Hypozalix) [24]. No objective measures were used in this study, however the visual analogue score showed a significant differences between the two treatment in lessening xerostomia symptoms. This study was considered at high risk of bias due to selective reporting (75 participants were allocated to the intervention but the results are reported only for the 62 completing the trial) and lack of blinding. Furthermore only statistical significance is reported in the text and the magnitude of benefit can only be approximated by the figure.

**Meta-analysis**

Four trials provided sufficient data to evaluate the primary outcome of the mean overall change in xerostomia symptoms. Six studies allowed statistical analysis of the assessment of changes in salivary flow rate. It was not possible to analyse the QoL outcomes due to differences in the outcome measures among the studies.

In relation to the primary outcome of reduction in xerostomia symptoms two comparisons were sufficiently clinically homogenous to perform statistical pooling: systemic pilocarpine vs placebo and systemic cevimeline vs placebo (Figure 3). Two studies, with no heterogeneity ($I^2$=6%) among them and a pooled total of 280 participants showed that the patients using pilocarpine for 12 weeks were more likely to have a 25mm or higher reduction in xerostomia VAS score compared to placebo (OR of 2·37, 95% CI 1·43-3·94). Two homogeneous studies ($I^2$=0%) with a pooled total of 563 participants showed that patients using cevimeline for 12 weeks were more likely to report an improvement in the sensation of xerostomia compared to placebo (OR 1·37, 95% CI 0·98-1·91).

In relation to the secondary outcome we were able to compare the effect of acupuncture vs sham/superficial acupuncture, cevimeline vs placebo, and

pilocarpine vs placebo on unstimulated salivary flow rates (Figure 4 and 5). Two studies of acupuncture versus sham/superficial acupuncture with no heterogeneity ($I^2$=0%) and a pooled total of 50 participants showed no increase (MD 0·00; 95% CI -0·02-0·03) in unstimulated/stimulated salivary flow rate. Pooled analysis of two RCTs of cevimeline versus placebo (total number of patients = 563) showed a small (MD 0·04, 95% CI 0·02-0·06) increase in unstimulated saliva flow rate in participants using cevimeline for 12 weeks with respect to controls. Two RCTs (total number of patients = 280) showed that the use of one tablet of pilocarpine is more likely to be associated with any short-term increase (60 minutes) in unstimulated salivary flow rate compared to one tablet of placebo (OR 2·27; 95% CI 1·37-3·76).

## DISCUSSION

No clear evidence-based guidance for clinicians is currently available to inform the management of radiotherapy-induced hyposalivation and xerostomia in HNC survivors. We have previously commented [13] on the questionable validity of the systematic review and meta-analysis of Lovelace et al [14] and the systematic review performed by Jensen et al [12] also seem to have similar weaknesses such as the inclusion of non-randomised studies and linguistic constraints [36, 37]. Other reviews focussed on single intervention [8-11].

In this multiple-treatment systematic review we have tried to overcome limitations of previous studies. Additionally we looked at a number of details of published trials (e.g. type of outcome, length of treatment, time of collecting outcome measurement) that were not highlighted in previous reviews but we believe are important for the interpretation of the efficacy of interventions. We included 20 RCTs with a total of 1732 randomized patients. Meta-analyses were only possible for three interventions because of the limited number of studies and their heterogeneous designs. Where data polling was possible, results suggest that long-term use of systemic pilocarpine or cevimeline has a positive effect in reducing xerostomia sensation in HNC survivors, with likelihood of improvement being higher for pilocarpine. However the effect size of such reduction was unclear for pilocarpine (at least 25mm on 0-100mm VAS) and not reported for cevimeline. It remains unknown whether a VAS change of at least 25mm is clinically relevant in this patient population, whereas the improvement in symptoms obtained with cevimeline do seem clinically meaningful (as patients reported to feel better/much better). Further, this positive effect seems to be limited to symptoms perceived shortly after the administration of the intervention, whilst no information is available with respect to dry mouth symptoms perceived under resting salivary conditions.

Pilocarpine and cevimeline also seem effective in increasing salivary flow. Our meta-analysis shows that long-term use of cevimeline can induce an increase in

unstimulated salivation, though the relevant effect size seems small (MD of 0·04 mL/min). However patients reported to feel better/much better and therefore a MD of 0·04mL/min may be considered clinical meaningful. With respect to pilocarpine, available data only provide evidence of a short-term increase in salivation with the use of one tablet (salivary flow measured after 60 minutes), whereas the effect size, clinical significance, as well as the effects of long-term use are unknown. Again no information is available with respect to salivary gland function under resting conditions.

With respect to acupuncture, data from our meta-analysis show no evidence of increased salivary flow and unknown effect upon dry mouth symptoms due to lack of data.

There results have practical implications as clinicians managing HNC survivors with post-radiotherapy hyposalivation and dry mouth symptoms should consider prescribing long-term cevimeline therapy and expect that it will provide some reduction in dry mouth symptoms and a small yet possible clinically meaningful increase in salivary flow, although likely to be short-lived. Similarly they should expect a reduction in xerostomia symptoms with long-term pilocarpine use, as well an increase in salivary flow after one tablet of pilocarpine, although these improvements are likely to have a short duration, unclear effect size, and unknown clinical significance. The toxicity of pilocarpine and cevimeline seems similar, possibly with a tendency for cevimeline to be better tolerated, although evidence is not robust as no direct comparison is available.

With respect to acupuncture, there was no evidence that it increases salivary flow, whereas it was not possible to pool data upon changes in dry mouth symptoms. Therefore, it seems difficult to support the clinical decision of recommending acupuncture in this patient population. With regard to interventions not included in the meta-analysis, there is no evidence, or very weak evidence, that “topical” pilocarpine, hyperthermic supersaturated humidification, acupuncture, herbal

medicine, ALTENS or LLT can reduce xerostomia symptoms, increase salivary flow, or improve QoL in this population.

Salivary substitutes and mouth care products are widely used in the management of xerostomia [12]. We found high heterogeneity among the six studies included in this paper and therefore no data pooling was possible. Our systematic review of single studies suggests that there is some weak evidence from 2 small studies, of which one is at high risk of bias, that enzyme-enriched mouth care products (gel and toothpaste) are superior to traditional carboxymethyl-cellulose gel and commercial toothpaste at reducing dry mouth symptoms and increase salivation. The effect size, where reported, seems to be small (23mm 0-100mm VAS) with unknown clinical significance. There is also some weak evidence from one small trial that among enzyme-enriched mouth care products, the more viscous one (BioXtra) can lessen dry mouth symptoms more than low-viscosity products (Oral Balance); however relevant effect size seems small (11·2mm difference on 0-100mmVAS) and clinical significance is unknown. With respect to the other three trials on salivary substitutes, there remains very weak evidence regarding the beneficial effects of an intra-oral device releasing Oral Balance gel, xanthan gum-based salivary substitutes, aloe vera gel, rape oil, or mucin spray upon dry mouth symptoms, salivary flow or QoL.

The present study has a number of limitations. The studies included in this review were conducted between 1993 and 2015. During this time the patient population has changed, and radiotherapy modalities have also changed, with participants of the most recent studies likely receiving lower radiation dosage to salivary glands. Also only summary data rather than patient level data were available.

## Conclusions

Pilocarpine and cevimeline should represent the first line of therapy in HNC survivors with radiotherapy-induced xerostomia and hyposalivation. There is very weak evidence that salivary substitutes can provide some, if any, benefit of small magnitude and unclear clinical significance. The use of other treatment modalities cannot be supported on the basis of current evidence.

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