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Review

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 randomised 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-analyzed.

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-analysis, 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 head and neck cancer survivors with radiotherapy-induced xerostomia and hyposalivation. The use of other treatment modalities cannot be supported on the basis of current evidence.

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

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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-Analyzes (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 07th of July 2016. Study inclusion criteria were (i) design: randomised 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 ($p < 0.05$).

Results

Fig. 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 min 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 min in two studies [17,18], and after 180 min 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 (Fig. 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 25 mm 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,