ADA CE Program ARTICLE 1

COVER STORY

Efficacy and safety of pilocarpine for radiation-induced xerostomia in patients with head and neck cancer

A systematic review and meta-analysis

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ABSTRACT

Background. Pilocarpine has been used widely in the treatment of dry mouth and glaucoma. In this review, the authors assessed the efficacy and safety of pilocarpine for patients with head and neck cancer who have radiation-induced xerostomia.

Types of Studies Reviewed. The authors conducted a systematic search including meta-analyses and randomized controlled trials in the following databases: MEDLINE, Embase, Cochrane Library, and Science Citation Index Expanded. The primary outcome was the severity of xerostomia (measured using visual analog scale [VAS] scores). Adverse events were other outcomes of interest. The authors performed meta-analyses where appropriate. The authors used the Cochrane Collaboration's tool for assessing risk of bias to assess the quality of the study.

Results. The authors identified 6 studies (including 752 patients in total). The results of a meta-analysis of 3 articles showed that pilocarpine was associated with a 12-point increase in VAS score (mean difference, 12.00; 95% confidence interval [CI], 1.93-22.08; $P = .02$) and higher rates of adverse events compared with placebo in terms of sweating (odds ratio [OR], 3.71; 95% CI, 2.34-5.86; $P < .00001$). There were no differences in rhinitis (OR, 1.21; 95% CI, 0.68-2.16; $P = .52$) and nausea (OR, 1.44; 95% CI, 0.83-2.49; $P = .19$).

Conclusions and Practical Implications. On the basis of the best available evidence, the results of this meta-analysis provide evidence that pilocarpine offers statistically significant clinical benefits for the symptomatic treatment of radiation-induced xerostomia in patients with head and neck cancer. However, the authors of this systematic review found the best available evidence in the meta-analysis in 3 studies, 1 of which showed no effect. The authors of this systematic review suggest that these patients take 5 milligrams of pilocarpine 3 times daily, and that there is need for further study.

Key Words. Meta-analysis; pilocarpine; xerostomia; radiotherapy; head and neck carcinoma.

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Head and neck carcinoma (HNC) is the sixth most common cancer worldwide, and it accounts for 2.8% of all malignancies.[1] Radiotherapy (RT) is the primary useful therapeutic option in the treatment of the HNC. However, xerostomia is a major adverse sequelae for patients who undergo RT. Xerostomia usually is defined as a subjective sensation of dryness of the oral mucous membranes,[2,3] and it can exert late effects on oral health, such as dry mouth, sore throat, altered taste, dental caries, as well as impaired function of chewing and swallowing.[4,5] Moreover, Shiboski and colleagues[6] and Del Regato[7] reported that severe xerostomia may prevent patients from returning to jobs that depend on direct communication.

Pilocarpine is a cholinergic parasympathomimetic agent that stimulates muscarinic cholinergic receptors on the surfaces of exocrine glands. This drug can relieve the symptoms of mouth dryness, even in patients

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with no measurable salivary flow at rest.[8-12] The results of some previous studies indicated that pilocarpine reduced the risk of radiation-induced xerostomia when it was given during RT.[13-15] However, the investigators of other randomized clinical trials did not observe this beneficial effect.[16-19] The reason for these conflicting results is still unknown.

We investigated the efficacy and safety of pilocarpine for the treatment of xerostomia in patients with HNC who received RT by integrating the results of available high-quality studies in the literature and by conducting meta-analyses.

METHODS

Study selection. We conducted a systematic literature search strategy to screen MEDLINE, Embase, Cochrane Library, and Science Citation Index Expanded (before July 2014) using medical subject headings (MeSH) to identify all original studies. We performed the search with no lower date limit, but we restricted the language used in the articles to English only. We also searched the reference lists of included studies to identify additional studies. We used the following MeSH terms—"pilocarpine," or "Pilocarpine Hydrochloride," "xerostomia," "radiotherapy," "head and neck carcinoma" or "head and neck neoplasms" or "cancer of the head and neck"—and we considered every possible combination. We made an effort to contact all corresponding authors for more information when data were missing.

Identification of articles and data extractions. None of the previously published meta-analyses presented data regarding xerostomia induced by radiation in patients with HNC. The authors of a few reviews reported the management of salivary dysfunction during and after RT, but the authors of these studies did not include recent randomized controlled trials (RCTs) and they did not perform meta-analyses.

We divided the selection and data extraction procedure into 3 phases and placed no restrictions on the search to maintain more specific methodological characteristics. In the first phase, the first author (C.-Q.C.) selected studies on the basis of the titles and abstracts, and then 2 independent investigators (the first and second author, C.-Q.C. and H.X.) screened all of the remaining abstracts to decide whether the study was consistent with the inclusion criteria. These investigators resolved disagreements for inclusion by mutual agreement. In the second phase, the same 2 investigators independently evaluated full articles using the same inclusion criteria as we describe in the next paragraph. In the third phase, the first author (C.-Q.C.) excluded articles whose authors did not include adequate data or whose results included duplicated research. Unfortunately, the authors of 3 articles reported inadequate data related to the visual analog scale (VAS) scores, and our requests for additional information were unsuccessful. Two independent investigators (C.-Q.C. and H.X.) extracted the data, including first author, publication year, original country, ethnicity, case number, type of design, medication dose, outcomes, and adverse effects, and they reached a consensus on all items through consultation.

Inclusion criteria. We collected the studies on the basis of the following eligibility inclusion criteria: the study's investigators compared the use of pilocarpine with the use of a placebo to treat xerostomia using quantitative outcome data; patients with the ability to produce moisture had at least 1 saliary gland, received a dose of radiation treatment (mean [standard deviation], 60 [15] gray), and did not have a history of irradiation in this region; and the investigators measured the severity of xerostomia using VAS scores (as indicated on a 100-millimeter scale).

Quality assessment of included studies. Two reviewers (C.-Q.C., Y.-T.L.) independently evaluated the methodological quality of the studies to access each of the included articles more accurately. We used The Cochrane Collaboration's tool for assessing risk of bias[20] in the review. Two reviewers (C.-Q.C., Y.-T.L.) assessed and scored the random sequence generation (selection bias), allocation concealment (selection bias), masking of participants and personnel (performance bias), masking of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). We judged each study to have a low risk of bias, a high risk of bias, or an unclear risk of bias.

Data synthesis and analysis. We performed meta-analyses on the severity of xerostomia. We used Review Manager 5.1 software from The Cochrane Collaboration to evaluate mean differences for VAS scores. We identified statistical heterogeneity by eyeballing (that is, visually inspecting forest plots) and using the χ^2 test for heterogeneity (a P value of .1 indicated significance) and the I^2 statistic as a measure of inconsistency across studies.[20] If the I^2 value was 30% or less, we used a fixed-effects model; if the I^2 value was between 31% and 60%, we used a random-effects model; and if the I^2 value was greater than 60%, we deemed that pooling would be inappropriate owing to a high level of statistical heterogeneity.[21] We also performed a sensitivity analysis; the main results had a high degree of similarity. Considering the relatively small sample size and the moderate level of heterogeneity,

ABBREVIATION KEY. **HNC:** Head and neck carcinoma. **HNRQ:** Head and Neck Radiotherapy Questionnaire. **LENT-SOMA:** Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic. **MeSH:** Medical subject headings. **RCT:** Randomized controlled trial. **RT:** Radiotherapy. **SSF:** Stimulated saliva flow. **USF:** Unstimulated saliva flow.