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Management of radiotherapy-induced salivary hypofunction and consequent xerostomia in patients with oral or head and neck cancer: meta-analysis and literature review

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Objective. To analyze the efficacy of various treatment options for radiation-induced hyposalivation in patients with head and neck cancer.
Study Design. A literature review and meta-analysis was performed on all appropriate literature identified via MEDLINE/PubMed.
Results. Fourteen articles were identified that met inclusion criteria for review, and 8 articles qualified for inclusion in the meta-analysis. The available literature addressed both objective and subjective responses of hyposalivation, xerostomia, or both to cholinergic agonists (such as pilocarpine and cevimeline), salivary substitutes, hyperbaric oxygen, and acupuncture.
Conclusions. This analysis indicated that cholinergic agonists were more effective in treating radiation-induced hyposalivation compared with salivary substitutes, hyperbaric oxygen, and acupuncture. However, other treatment modalities, such as salivary substitutes and hyperbaric oxygen, were also found to subjectively improve patients' perception of xerostomia. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;■:1-13)

An estimated 53,640 new cases of cancer of the oral cavity, pharynx, and larynx were projected to arise in the United States in 2013, resulting in 11,520 deaths.[1] Head and neck cancer is commonly treated by combinations of surgery, radiation therapy, and chemotherapy. Of these treatment modalities, radiation therapy is often associated with both acute and long-term complications, including mucositis, dysphagia, hoarseness, erythema, desquamation of the skin, and xerostomia.[2] Type and severity of complications are related to radiation dose, radiation field, and duration of treatment. Inevitably, radiation induces cytotoxic injury to the salivary glands, resulting in dysfunctional acinar cells that, despite regeneration, do not function normally.[3,4] These defects in cellular functioning result in salivary hypofunction and consequent acute and chronic xerostomia.

Salivary hypofunction, the objective decline in salivary flow, is often accompanied by xerostomia, the subjective perception of dry mouth, in patients with head and neck cancer that have received radiation therapy. In fact, patients who receive radiation therapy are 6 times more likely to develop salivary hypofunction and xerostomia than the general population.[5] Healthy adults produce 1000 to 1500 mL of saliva daily, with 90% contributed by the major salivary glands.[6] Conventional radiation therapy for the treatment of head and neck cancer generally includes daily fractions of 1.8 to 2.0 Gy, with total doses up to 50 to 70 Gy over a 5- to 7-week period.[7,8] However, studies have found that a mean dose of 20 to 40 Gy to the parotid gland results in significant reduction in stimulated salivary flow, rendering it nearly undetectable.[9,10] There is a 50% to 60% decrease in salivary flow during the first week, which is reduced to 20% by week 7 of conventional radiation therapy.[11]

Although radiation damage to salivary glands is a well-described entity, the exact mechanism of damage has yet to be fully determined. Animal model studies have found that within the first few days of radiation treatment, no cell loss is observed within the glands. However, as treatment progresses, damage to the plasma membrane of acinar cells results in disruption of intracellular signal transduction, ultimately causing a change in salivary composition. In addition, radiation causes destruction of progenitor cells and stem cells, rendering acinar cells nonfunctional over time. Some regeneration can occur, but function generally remains impaired indefinitely owing to damage to blood vessels,

Statement of Clinical Relevance

Radiation-induced hyposalivation results in acute and long-term complications that can negatively affect oral health and quality of life. Clinicians should be aware of the severity of the condition and be able to identify and offer effective treatment options to patients.

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ducts, and nerves.[3,4] Similar studies in humans have found results consistent with these findings.[12]

Radiotherapy to the head and neck can result in a reduction in salivary flow rates, decreased saliva pH, and altered saliva consistency.[2] These changes may induce symptoms of oral burning or soreness, halitosis, changes in taste acuity, impaired deglutination, mastication, and phonation, increased risk of dental caries and osteoradionecrosis, denture discomfort and loss of retention, bacterial sialoadenitis, and increased susceptibility to infection of the oral cavity and oropharynx by the opportunistic fungus *Candida albicans*.[5,13] Some patients see improvement of radiation-induced hyposalivation and xerostomia within 12 to 18 months after radiation therapy, depending on dose and volume of irradiated gland tissue.[14,15] However, most patients do not see significant change over time, causing salivary hypofunction to be a life-long radiation morbidity that has major effects on oral health and quality of life (QOL).

Given the high rate of development of hyposalivation and xerostomia after radiation therapy, investigators have researched both prevention and treatment options. Prevention options include radiation delivery techniques such as intensity-modulated radiotherapy and 3-dimensional conformal radiotherapy, which aim to minimize dosage and spare adjacent tissues. Other prevention interventions include salivary gland transfer, cytoprotectants such as amifostine, and pilocarpine administered during radiation therapy.[16,17] These studies, however, have found varied success rates and potential adverse effects, increasing the urgency to identify effective treatment options once xerostomia has developed. Treatment options include muscarinic acetylcholine agonists, such as pilocarpine and cevimeline; salivary substitutes; mechanical, gustatory, and electrical salivary stimulants; bethanechol; acupuncture; and hyperbaric oxygen therapy (HBOT).[18-25] Despite much investigation, there remains no clear treatment option for radiation-induced xerostomia. Thus, the aim of this study was to analyze postradiotherapy treatment options for radiation-induced hyposalivation and xerostomia to determine which management strategies improve the condition and to identify the optimal treatment option for these patients with head and neck cancer.

METHODS

A systematic review of the literature was performed using the database of MEDLINE/PubMed to search for articles published in English that addressed treatment options for radiation-induced xerostomia in patients with head and neck cancer. For each article, information regarding study design, study population, cancer treatment modality, treatment option, method of xerostomia measurement and definition, results, and conclusions was recorded.

Search strategy

The electronic database of MEDLINE/PubMed was searched for articles using selected keywords related to salivary hypofunction and xerostomia in patients with head and neck cancer. Sources were limited to clinical trials of phases I to IV, randomized controlled trials, comparative studies, and controlled clinical trials published in English. Gender and age were not limited.

An initial search was conducted using the terms [xerostomia] AND [head and neck cancer]. Additional searches included the terms [xerostomia] OR [hyposalivation] OR [salivary hypofunction] OR [dry mouth] AND [radiation therapy] OR [chemoradiation] OR [oral cancer] OR [oropharynx cancer] OR [pilocarpine] OR [bethanechol] OR [cevimeline] OR [saliva substitutes] OR [acupuncture] OR [hyperbaric oxygen] OR [gustatory stimulant] OR [mechanical stimulant] OR [electrical stimulant]. References from all identified studies were searched to identify any supplementary sources.

Selection criteria

Inclusion criteria included articles that treated radiation-induced hyposalivation and xerostomia, defined as agent or procedure initiated after radiation therapy. To be included for systematic review, studies must have reported data from prospective controlled clinical trials, patients with head and neck cancer treated with radiation therapy of at least 35 Gy, minimum sample size of 10, and hyposalivation/xerostomia as a primary or secondary endpoint. Exclusion criteria included incomplete studies that did not report actual data, studies with relevant follow-up publications, studies with only animal models, studies with only QOL data, etiology of hyposalivation/xerostomia other than radiation therapy, novel treatments such as intraoral devices, gene transfer, stem cell transplant therapy, and articles published before 1990.

The Jadad questionnaire was used to determine the quality of clinical trials and limit bias.[26] Using this 3-item validated scale, 11 of the 14 studies included in the review received a score of 4 or 5. Two studies received a score of 3, and 1 study received a score of 1.

Data extraction

Data from each study meeting inclusion and exclusion criteria were extracted independently by 2 authors into a standardized database and cross-checked for accuracy. Information extracted from each study included author, year of publication, number of patients, type of