Management of Radiation Induced Xerostomia

Clinical Significance

Xerostomia describes both the subjective sensation of oral dryness and the objective reduction in salivary function. Most oncology patients experience oral dryness, at least temporarily during the trajectory of their illness and treatment. In fact, almost all head and neck cancer patients undergoing radiotherapy experience some degree of xersostomia (Chambers, Rosenthal & Weber, 2007). Inadequate salivary function creates multiple complications, including poor dentition, a propensity to oral infections, sleep disturbances, oral pain, and difficulty talking, chewing and swallowing (Deasy et al., 2010). Radiation therapy is the most common source of treatment-related xerostomia in cancer. The degree of permanence and severity directly correlates with the amount of radiation dose delivered to the salivary glands (Deasy et al., 2010). The use of concurrent chemo-radiation compounds damage to salivary glands and increases the risk of long-term salivary dysfunction (Bhide, Miah, Harrington, Newbold & Nutting, 2009). Concurrent chemo-radiation dramatically increases the incidence of salivary gland dysfunction (by about 70%) when compared to radiation alone (Bhide et al., 2009). In addition, agents including 5-fluorouracil, cisplatin, bleomycin, methotrexate, doxorubicin, cyclophosphamide, and vinblastine are all independently associated with dry mouth (Camp-Sorrell, 2005).

Xerostomia has a profound negative impact on quality of life. The lack of salivary secretions impacts the ability to eat, sleep, speak, and swallow (Lew & Smith, 2007). A dry mouth can lead to taste changes, which in turn decreases appetite and can lead to subsequent weight loss and malnutrition (Lew & Smith, 2007). Patients with xerostomia have difficulty with dry or thick food, and their meals are frequently interrupted with sips of fluid to aid chewing and swallowing (Bhide et al., 2009). Xerostomia increases the risk for dental caries, enamel erosion and other dental defects as saliva has antimicrobial properties (Wu, 2008). Saliva also aids with the retention, stability and comfort of dentures. Therefore, xerostomia leads to denture instability and increased difficulty chewing (Arslan, Orhan, Canpolat, Delilbasi, & Dural, 2009). Xerostomia affects the ability to sleep, as rest is frequently interrupted due to oral dryness. The patient may awake frequently with the tongue adhered to the hard palate and the need to expectorate frequently or manually remove thick saliva. (Bhide et al., 2009).

Pathophysiology

Salivary Glands

The major salivary glands are the parotid, submandibular, and sublingual. Additional minor glands are unnamed and vary in distribution throughout the oral cavity and pharynx. The parotid and the submandibular glands are the main contributors to salivary flow, contributing approximately 90% of salivary volume (Vinagre, Santos, Prata, Canas da Silva, & Santos, 2009). The secretory unit of the salivary gland is constructed of acinar cells, myoepithelial cells, intercalated ducts, striated ducts and excretory ducts (Camp-Sorrell, 2005). The acini are responsible for secreting serous and mucous constituents of saliva. The parotid gland produces purely serous secretions, creating watery saliva, while the submandibular and sublingual glands produce predominantly mucous secretions, which are more viscous (Camp-Sorrell, 2005). Therefore, the site of glandular injury dictates the functional change in the saliva and subsequent symptoms. The secretions from acini travel through the collecting ducts and are emptied into the oral cavity. In the average individual, about one liter of saliva is produced daily, about 60% of which is from the parotid glands, 20% from the submandibular and 5% from the sublingual (Arslan et al., 2009). Secretory function is stimulated by taste, smell, chewing and other psychological factors as well as stimulation from other organs such as the esophagus and the stomach (Bhide et al., 2009).

Saliva

Saliva is comprised of 90% water and exerts antimicrobial, digestive, antacid, and lubricative properties (Ikebe et al., 2006; Lew & Smith, 2007). Saliva prepares food for mastication, swallowing, and normal taste perception (Arslan et al., 2009). The flow of saliva aids in the clearance of sugars and carbohydrate remnants, thus protecting dental enamel (Hahnel, Behr, Handel & Bürgers, 2007). Salivary flow lubricates the soft tissues, protecting the mucosa and gingiva from desiccation, penetration and ulceration (Ikebe, Morii, Matsuda, Hata, & Nokubi, 2005). Saliva also stimulates soft

tissue repair by reducing clotting time and accelerating wound contraction. Active salivary flow prevents infection by decreasing bacterial and candidal activity (Ikebe, Morii, & Matsuda et al., 2006).

Radiation-induced Xerostomia

Glandular damage and long term loss of function is directly related to the amount of radiation exposure. Salivary flow reduces to 50–70% of baseline after 10–16 Gy radiation and is undetectable after 40–42 Gy radiation (Bhide et al., 2009). Radiation-induced damage to the salivary glands alters the volume, consistency and pH of secreted saliva (Pow et al., 2006). The secretions become more tenacious and acidic during radiotherapy. After whole parotid irradiation with conventional radiotherapy techniques, there is little long-term recovery. However, with intensity-modulated radiotherapy (IMRT), long-term recovery of salivary function has been reported to occur up to 2 years after the completion of treatment (Pow et al., 2006).

Severe chronic xerostomia, defined as a long-term salivary function of <25% of baseline, can be avoided if at least one parotid gland is spared to a mean dose of less than 20 Gy, or if both glands are spared to less than 25 Gy (Anand et al., 2006). Sparing of the submandibular gland significantly decreases the risk of xerostomia. The necessity of treating bilateral cervical lymph nodes in most head and neck cancer patients makes it difficult to spare even one parotid gland using standard three-dimensional conformal radiotherapy (Bhide et al., 2009). Intensity-modulated radiotherapy has significantly better long term outcomes than conformal radiotherapy as it can spare parotid glands and thus improves quality of life (Anand et al., 2006).

Clinical Presentation

The goal of assessment is to manage acute symptoms and evaluate for late and chronic effects. The presentation in both acute and chronic cases includes functional alterations such as speech and swallowing difficulties, and subjective complaints including gagging sensations, a fear of choking, odynophagia (painful swallowing), and the inability to swallow foods and liquids with varying consistencies (Camp-Sorrell, 2005).

In acute xerostomia (i.e. occurring concurrent with or immediately after radiation therapy), the patient may experience dry oral mucosa and thick, sticky copious oral secretions (Bhide et al., 2009). Upon exam, the patient may have halitosis secondary to food stagnation on the oral mucosa, gingiva, teeth or tongue (Mese & Matsuo, 2007). Dysgeusia (abnormal taste) commonly accompanies xerostomia. Taste loss during active radiotherapy to the oropharynx is also expected, as saliva has a role in mediating taste, and occasionally patients will display residual long-term or permanent hypoguesia (Mese & Matsuo, 2007). Glossodynia (burning tongue) also commonly accompanies xerostomia. The tongue can become dry, depapillated, and fissured and may be described as burning and itchy (Camp-Sorrel, 2005). The damage to the dorsal epithelium leads to the tongue becoming atrophic or eroded and erythematous. Chelitis, a fissuring or ulceration in the angles of the mouth, occurs frequently in xerostomia and may be noted on presentation (Camp-Sorrell, 2005).

In addition to the clinical sequelae seen in acute cases, chronic xerostomia exhibits recurrent oral infections, the deterioration or atrophy of the oral epithelium and painful excoriation and ulceration. Candida and other oral infections common to the tongue or buccal mucosa (Ikebe et al., 2006) are widely seen. Dental manifestations such as dental caries and periodontal disease commonly occur (Arslan et al., 2009). Many patients with chronic xerostomia ultimately lose all of their teeth to decay, negatively affecting quality of life for long-term survivors.

Deasy et al. (2010) state that xerostomia can be diagnosed according to the patient’s symptoms, such as altered taste or sensations of dryness or quantified by saliva production. Wu (2008) outlined a physical exam when assessing for xerostomia:

Observe the face for fullness suggestive of salivary gland enlargement. Listen to the patient's speech and assess for a smacking sound of the dry oral mucosa sticking to the teeth. Observe the lips for dryness, fissuring, erythema, ulceration, and swelling. Examine the oropharynx starting with the labial mucosa, the buccal mucosa, the hard/soft palate, the gingiva, the tongue, and the floor of mouth. A piece of gauze may be used to dry the floor of the mouth to assess for the pooling of saliva as it exits the submandibular and sublingual glands. Note salivary expression from the right and left parotid papillae. Note the quality as clear, cloudy, or thickened; hanging droplets of saliva indicate increased viscosity of the saliva.

Although a patient can be diagnosed based on clinical presentation and symptoms, diagnostic imaging may be useful to quantify functional status of the glands which may direct treatment interventions. Sialography is a procedure in which a catheter is inserted through the mouth and into the duct of a salivary gland (Vinagre et al., 2009). A contrast medium is then injected into the duct and x-rays obtained to quantify gland function. This technique is performed by radiology, and is reproducible and well tolerated by patients (Vinagre et al., 2009). Ultrasound of the salivary glands is another available diagnostic option. Ultrasound is a useful to visualize glandular structural changes in patients (Salaffi et al., 2008).

An appropriate differential diagnosis is important to correctly diagnose and treat xerostomia. Oral candiasis, poor oral hygiene, medication-induced toxicities, and mucositis should all be considered as potential alternative diagnoses.

Management Strategies

The goal of treatment is the provision of moisture and lubrication by stimulating functional glandular tissue or by salivary replacement with oral lubricating agents. The treatment of secondary conditions like infections, the prevention of oral and dental disease, and the provision of nutritional support are imperative to quality care. Strategies for treatment include combinations of gustatory and pharmacologic methods to increase salivary flow. Interventions include antibacterial mouthwashes, topical fluorides, oral buffering products, artificial saliva or moisturizing sprays or rinses, and remineralizing products (Wu, 2008).

Pharmacologic Prevention

The most widely studied salivary gland cytoprotectant is Amifostine. The use of Amifostine may be considered to decrease the incidence of acute and late xerostomia in patients undergoing radiation therapy alone for head and neck cancer (Bhide et al., 2009; Hensley et al., 2009). Amifostine acts as a radioprotectant by scavenging free radicals to protect subcellular structures from damage by the radiation treatment. The ability for Amifostine to have selective uptake is debated, however, and there is fear that the mechanism of action is tumor-protective. Amifostine also has significant side-effects which limits tolerability, including hypotension, nausea, vomiting and allergic reactions (Hensley et al., 2009). The risks versus the potential benefits of Amifostine use must be weighed with each patient.

Proton therapy is a promising targeted radiotherapy with the possibility of glandular sparing. Proton therapy can minimize the radiation dose to surrounding normal tissues while at the same time delivering tumoricidal dose to the tumor target (Chan & Liebesh, 2008). Research indicates that it may be more effective and less harmful than other forms of radiation therapy (Chan & Liebesh, 2008). However, proton therapy is not yet widely available and randomized clinical trials comparing it to other types of radiation are just beginning. According to the National Association for Proton Therapy (2010) currently there are only 7 centers in the United States and 4 under construction.

Pharmacologic Treatment

Salivary stimulants such as Pilocarpine (SalagenÒ) and Cevimeline (EvoxacÒ) are the most widely studied pharmacological interventions for xerostomia. Pilocarpine is an oral salivary stimulant which is effective and well tolerated in the treatment of radiation-induced xerostomia (Chitapanarux et al., 2008). Pilocarpine is a parasympathomimetic agent that functions primarily as a muscarinic agonist with mild beta-adrenergic activity (Chitapanarux et al., 2008). This causes the pharmacological stimulation of exocrine glands in humans and among its effects is increased salivation. (Bhide et al., 2009). Cevimeline is an acetylcholine analogue that selectively stimulates the muscarinic receptors found in salivary glands and has a longer half-life and duration of action than pilocarpine (Chambers et al., 2007). Cevimeline is well tolerated by patients with xerostomia after radiotherapy for head and neck cancer, and consistently improves unstimulated salivary flow (Chambers et al., 2007).

Non-Pharmacologic Interventions

A multitude of non-pharmacological interventions can mitigate the symptoms of xerostomia. Dental care and surveillance are extremely important to prevent caries. Patients should use soft tooth brushes and fluoride toothpaste while avoiding products which contain sodium lauryl sulfate, which increases mucosal irritation. The use of fluoride gels and rinses with bicarbonate to increase pH in the oropharnyx should be considered to further protect tooth enamel (Wu, 2008). Frequent mouth care throughout the day, including the use of saline rinses, and sponge sticks,

may also be effective in helping protect the teeth. Saliva substitutes include products such as Xero-lubeTM, OptimoistTM or simply water. Studies have demonstrated variation amongst product efficacy, which should be noted (Hahnel et al., 2009; Mouly et al., 2007). The daily use of topical dry mouth products containing olive oil, betaine and xylitol are safe and effective in relieving symptoms of dry mouth (Ship, McCutcheon, Spivakovsky, & Kerr, 2007). Meat tenderizers administered in aqueous solution or papaya, which both contain the enzyme papain, can help reduce the thickness of secretions (Camp-Sorrell, 2005). Alcohol, tobacco and large amounts of caffeine should be avoided as they have a drying effect and can exacerbate symptoms (Camp-Sorrell, 2005). If glossodynia is present, spicy and acidic foods should be avoided as they can increase discomfort (Camp-Sorrell, 2005). Citric acid and acidic beverages can be helpful in stimulating salivation, although they can also cause erosion of tooth enamel and should therefore be used with caution (da Mata et al., 2009). Mastication will stimulate secretion if there is functional glandular tissue (Mese, & Matsuo, 2007). Therefore, vigorous chewing several times a day can be helpful and should be encouraged. Maintaining adequate nutrition can be challenging in the presence of xerostomia. The most easily managed foods are typically soft and high in carbohydrates. Patients should be encouraged to avoid sweet sticky foods and may benefit from a nutritional consult. It may be helpful to add butter, mayonnaise, yogurt or sauces to moisten foods. Take a sip of a liquid after each bite to help chewing and swallowing. Suggest that patients always carry water with them and keep themselves well hydrated. A mouth guard has been shown to be helpful in alleviating nocturnal symptoms of xerostomia (Yamamoto et al., 2008). Humidity has also been shown to be mildly beneficial in the form of a bedside vaporizer or household humidifier to reduce oral dryness (Yamamoto et al., 2008).

Acupuncture significantly improves stimulated and unstimulated salivary flow rates (Bhide et al., 2009). It is theorized that acupuncture stimulates the parasympathetic nervous system, resulting in an increase in the local blood flow to the salivary glands, increasing salivary production and possible regeneration of tissue (Jung et al., 2008; Wong, 2008). Another possible mechanism of action of acupuncture is stimulation of minor salivary glands present in non-irradiated buccal mucosa. Further research of acupuncture is necessary prior to the recommendation for widespread clinical implementation in xerostomia treatment (Bhide et al., 2009; Jung et al., 2008; Wong, Ahuja, Yuen, & King, 2003).

Conclusion

Chronic xerostomia is a challenge both for the patient and for the care provider managing their symptoms. Xerostomia is an unfortunately prevalent and distressing side effect of cancer treatment. Poor dentition, a propensity for oral infections, sleep disturbances, odonophagia, dysphagia and speech disturbances severely impact a patient's quality of life. Despite the few medical management options for prevention and treatment presently available, there are a multitude of effective non-pharmacological options that can be utilized in combination toward a goal of providing the utmost relief of symptoms for the patient. The emergence of proton beam therapy and potential decrease in the prevalence of xerostomia will hopefully lessen the burden of these distressing symptoms on cancer patients.

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