Radiotherapy Induced Xerostomia in Head and Neck Cancer Patients

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***Abstract*- Introduction:** Head and neck cancers constitute 5% of all cancers worldwide with an annual incidence of about 5,00,000 cases of which two-thirds are locally advanced. Radiotherapy with or without chemotherapy forms an integral part of the multimodal management. Seven to eight weeks treatment is accompanied by its acute & late reactions, of which xerostomia is one of the major complications of Radiotherapy.

With concurrent chemo-radiation, there is an increased incidence of salivary gland dysfunction (by about 70%) when compared with radiation alone. Inadequate salivary function creates multiple complications, including dental caries, a propensity to oral infections, sleep disturbances, oral pain, and difficulty talking, chewing and swallowing. Xerostomia has a profound negative impact on quality of life.

Dose-Response: The degree of permanence and severity of xerostomia directly correlates with the amount of radiation dose delivered to the salivary glands.

Measurement of Xerostomia: The Visual Analogue Scale, Zimmerman Xerostomia Questionnaire, LENT SOMA (Late Effect of Normal Tissues Subjective Objective Management Analysis) Scale, Salivary Gland Secretory Ratio (SGSR), determined by dynamic salivary 99^{m}Tc scintigraphy are some of the methods to find and grade the severity of xerostomia.

Treatment: The goal of treatment is the provision of moisture and lubrication by stimulating functional glandular tissue or by salivary replacement with oral lubricating agents. Interventions include sialogogues, antibacterial mouthwashes, topical fluorides, oral buffering products, artificial saliva or moisturizing sprays or rinses, and remineralizing products.

Prevention: Newer radiotherapy techniques like IMRT are being used to minimize the xerostomia. Drugs like amifostine and pilocarpine have been shown to increase salivary flow when used concurrently with Radiation therapy. Surgical transfer of submandibular gland to submental space (Glandulopexy) is another strategy employed to prevent xerostomia.

Conclusion: Xerostomia is important acute and late sequelae of radiation therapy leading to lot of patient anxiety and morbidity. The long-term impact of the newer techniques of Radiotherapy like IMRT, IGRT or Adaptive RT, newer drugs, acupuncture, gene therapy and alternative treatments is yet to be discovered.

***Index Terms*-** Xerostomia, Radiotherapy, Head and neck cancer, Saliva, Amifostine, Pilocarpine

I. Introduction

Head and neck cancer mainly comprises squamous cell carcinoma of mucous membrane of upper aerodigestive tract. Head and neck cancers, among the 10 most frequent cancers in the world, constitute 5% of all cancers worldwide with an annual incidence of about 5,00,000 cases of which two-thirds are locally advanced. Radiation therapy forms an integral component of the multimodal management of the disease. A definitive course of radiation therapy in head and neck carcinoma extends for about 6-7 weeks and is accompanied by its acute & late reactions. [1]

Xerostomia describes both the subjective sensation of oral dryness and the objective reduction in salivary function. Xerostomia is one of the major complications of Radiotherapy. In fact, almost all head and neck cancer patients undergoing radiotherapy experience some degree of xersostomia. Its incidence varied in the range of 60 to 93% in the era of conventional radiotherapy. With concurrent chemo-radiation, there is an increased incidence of salivary gland dysfunction (by about 70%) when compared with radiation alone. [2, 3]

Pathophysiology: The major salivary glands are the parotid, submandibular, and sublingual. The parotid and the submandibular glands are the main contributors to salivary flow, contributing approximately 90% of salivary volume. The parotid gland produces purely serous secretions, creating watery saliva, while the submandibular and sublingual glands produce predominantly mucous secretions, which are more viscous.

The parotid and the submandibular glands are the main contributors to salivary flow, whereas several minor salivary glands present in the oral cavity and the pharynx are minor contributors, secreting less than 10% of the saliva. The parotid gland is a purely serous-secreting gland, whereas the submandibular is predominantly serous. In the unstimulated state, the submandibular gland produces most of the saliva, whereas in the stimulated state the parotid gland is responsible for most of the saliva produced. Total salivary flow can be up to 1.5 liter a day in healthy person.[4]

Radiation-induced damage to the salivary glands alters the volume, consistency and pH of secreted saliva. The secretions become more tenacious and acidic during radiotherapy.

Animal studies led us to believe that radiation damage occurs in four distinct phases. Phase I (0-10 days) in which there is depletion of the water component but no effect on the acinar cells or on amylase secretion. Phase II (10-120 days) in which the acini suffer membranous degradation and loose the ability to

secrete amylase. Phase III (120-240 days) this marks the phase of late toxicity which is characterized by loss of functional acinar cells due to loss of progenitor stem cells. Phase IV marks the regenerative phase but the functional deterioration continues due to the damage to ducts nerves and vessels. [5]

Leslie and Dische. showed that salivary amylase became undetectable by 10th day of radiation due to acinar damage.[6]

Saliva is comprised of 90% water and exerts antimicrobial, digestive, antacid, and lubricative properties. Inadequate salivary function creates multiple complications, including dental caries, a propensity to oral infections, sleep disturbances, oral pain, and difficulty talking, chewing and swallowing. Xerostomia has a profound negative impact on quality of life. Rydholm and associates conducted a study to explore the global effects of xerostomia, with a specific focus on psychological and social consequences. Four main categories were identified in the study: Subjective discomfort, e.g. dryness or burning sensation, Loss of function, e.g. articulation or swallowing, Increased infection, (oral thrush and ulcerations), Psychosocial effects, including shame, increased feelings of being a patient rather than a person and a tendency to avoid social contact, resulting in loneliness. Xerostomia and its associated symptoms have a considerable, negative global impact, resulting in shame, anxiety, disappointments and verbal communication difficulties. There should therefore be more focus on the management of xerostomia, which is often neglected in palliative care.[7]
Xerostomia patients exhibit reduced ability to process food. The observed decline in masticatory performance is probably due to reduced activity of the muscles of mastication.[8]

II. Dose-response

The degree of permanence and severity of xerostomia directly correlates with the amount of radiation dose delivered to the salivary glands. Salivary flow reduces to 50–70% of baseline after 10–16 Gy radiation and is undetectable after 40–42 Gy radiation. Some recovery of function occurs with time, with the tissue dose required for a 50% response (TD50) increasing (i.e. more dose needed for the same level of injury) at longer follow-up times.[9]

The effects of fraction size on xerostomia are limited and conflicting. The α/β ratio for parotid has been estimated to be close to 20 in rats.

Contrary to this it is believed from the continuous hyperfractionated accelerated radiotherapy. (CHART) experience that hyperfractionation is protective for late effects.[10]

This may lead us to believe that the α/β ratio should infact be much smaller. Thus, it is believed that fractionation may have an impact on xerostomia with the salivary gland having a differential α/β ratio.[11]

III. Measurement of Xerostomia

The assessment of severity of xerostomia is done by subjective and objective techniques. The Visual Analogue Scale, Zimmerman Xerostomia Questionnaire, LENT SOMA (Late Effect of Normal Tissues Subjective Objective Management Analysis) Scale are some of the methods to find and Grade the severity of xerostomia. The salivary gland secretory ratio (SGSR), determined by dynamic salivary 99mTc scintigraphy and measurement of salivary output flow are an objective measure of salivary gland function.[12]

Prevention: Radiotherapeutic management is a challenge in head and neck due to the close proximity of the tumor and avoidance structure (esp. salivary glands).

In patients receiving definitive conventional radiotherapy grade-2 xerostomia is seen in 80% of patients while in only 30% of patients receiving focused radiation treatment like definitive Intensity Modulated Radiation Therapy (IMRT). [13, 14]

At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy (20 [83%; 95% CI 63-95] of 24 patients given conventional radiotherapy vs nine [29%; 14-48] of 31 given IMRT; $p<0{\cdot}0001$). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. 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. Intensity-modulated radiotherapy has significantly better long term outcomes than conformal radiotherapy as it can spare parotid glands and thus improves quality of life.[15]

Amifostine works on the principle of radio-protection and has been to reduce acute and chronic xerostomia. Demonstration of a tumor protective effect by some and the lack of benefit in the setting of chemoradiation by others. This led to the recommendations of the American Society of Clinical Oncology which advised against its use in the setting of chemoradiation (standard of care in head and neck tumor). [16, 17]

Pilocarpine is a parasympathomimetic sialogogue and has been shown to increase salivary flow when used concurrently with Radiation therapy. Even though Fisher et al demonstrated some improvements in salivary flow at 3 to 6 months, both Warde and Fisher failed to demonstrate any improvements in quality of life of patients. [18, 19]

Surgical transfer of submandibular gland to submental space (Glandulopexy) is another strategy employed to (outside the radiation field) preserve its function and prevent the development of radiation-induced xerostomia.[20]

IV. Treatment

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 approach is palliative. 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 sialogogues, antibacterial mouthwashes, topical fluorides, oral buffering products, artificial saliva or moisturizing sprays or rinses, and remineralizing products. Acupuncture has been reported to significantly increase the stimulated and

unstimulated salivary flow rate. Gene therapy is still at an experimental stage.

V. Supportive Measures

Better oral hygiene

As the physical stimulation of salivary glands originate in taste buds. Mechanical debridment of dorsum of tongue with soft tooth brush and use of spray misters before and during meal assists in maintaining access to taste buds. Oral Hygiene also reduces incidence of oral candidiasis.

Dental check-up

Nieuw and associates recommended in a study that after the radiation therapy is ended, a dental check-up should be done every 3 months to allow control of any incipient oral inflammation and dental decay.[21]

Antifungal prophylaxis

Use of antifungal lozenges and oral hygiene also helps.

Vitamin supplements

Patients should be advised to maintain a balanced diet and avoid foods that irritate unprotected saliva Vitamin A and Nicotinic acid supplements are known to increase salivary flow.

VI. Salivary Substitutes

Most of the patients use water for their symptom relief. There are many types of salivary substitutes available in the market. Salivary substitutes give only temporary relief like, Mucin containing sprays, Biotene, Sugar-free chewing gum, Lactoperoxidase, and glucose oxidase (Oral Balance) gel, Hydroxy-Propyl-Methyl-Cellulose (HPMC) etc.[22]

VII. Salivary Stimulants

Pilocarpine has become the focus of most clinical trials investigating salivary stimulants for the treatment of radiation-induced xerostomia. The recommended dose of pilocarpine is 5 mg three times daily. There was a significant improvement of salivary flow rate and quality of life in pilocarpine. Most common side effect of pilocarpine is sweating. It is contraindicated in bronchospasm, congestive heart failure, chronic obstructive pulmonary disease and acute bronchial asthma and acute congestive glaucoma. The maximum therapeutic effect is normally observed after 4 to 8 weeks of therapy.[23]

In Head and neck cancer patients when given concomitant with RT tablet Pilocarpine (5mg) three to four times a day is usually started three days prior to RT and continued for three months. In a double blind, placebo controlled study Average xerostomia score for patients who received pilocarpine was 68 mm and in group, which was not treated with pilocarpine, was 34 mm. The pilocarpine group attained statistical superiority in all assessment comparisons individually and with the average of the combined assessments ($p<0.01$)[24]

Cevimeline is now being evaluated for radiation-induced xerostomia. It has no cardiorespiratory side affect as that of pilocarpine.[25]

Blom et al reported that stimulated and unstimulated salivary flow rates were significantly better after 12 to 24 weeks of acupuncture. With the use of codetron, There was a significant improvement in the reported xerostomia (using the visual analog scale) and stimulated and unstimulated salivary flow rates. There was, however, no improvement in the patients' QoL. [26, 27]

Animal experiments have attempted to improve post-radiation salivary function by attempting to transfer genes coding for water channels in the acinar cells and genes coding for enzymes that mop up the free radicals produced during radiation. The techniques promises hope for future. [28]

VIII. Conclusion

Xerostomia is an important acute and late sequelae of radiation therapy leading to lot of patient anxiety and morbidity. Treatment of resultant dry mouth is at present poor. Important advances have been made in the understanding of the dose response of salivary glands and prevention and treatment of xerostomia. However, the long-term impact of the newer techniques of Radiotherapy like IMRT, newer drugs, gene therapy and alternative treatments is yet to be discovered.

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