REVIEW ARTICLE

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Current Trends in the Management of Xerostomia: A Review

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ABSTRACT:

Xerostomia is subjective sensation of dry mouth due to reduced salivary flow. Mouth dryness interferes with chewing, swallowing, speaking, with significant increase in dental caries and other oral infections that may have considerable impact on oral health. Dry mouth may be caused by systemic diseases, drugs or by radiotherapy of head and neck cancers, etiology being multifactorial, it affects nearly half of elderly and one fifth of younger age group.Treatment of xerostomia presents as clinical challenge to the oral physicians. Although some treatment have been used to improve the symptoms of xerostomia, none is satisfactory. This review aims to present, current trends in the management of xerostomia.

Keywords: Dry mouth, Hyposalivation, Xerostomia.

INTRODUCTION

Saliva plays a vital role in maintaining physiological homeostasis of the oral cavity. In addition to humidifying the oral tissues, its lubricating properties aid in swallowing, talking and also prevent damage due to mechanical agents.[1]

Xerostomia so called as dry mouth results from absent or reduced salivary flow. This term was derived from Greek word 'xeros' (dry) and 'stoma' (mouth).[2] On a worldwide basis, millions of people are affected by xerostomia. This condition can affect speech, chewing, swallowing, taste acuity, and ultimately the quality of life. Xerostomia affects approximately 20% of the elderly. Anxiety, mouth breathing, advancing age are precipitating factors.[3] Xerostomia decreases the oral pH and increases the susceptibility to periodontal disease and dental caries.[4] Glossitis, cracked peeled atrophic lips, progressive cusp tip caries, pale corrugated dry buccal mucosa and candidiasis are major symptoms encountered in xerostomia.[5]

ETIOLOGY OF XEROSTOMIA

The prevalence of xerostomia in general population vary and is seen predominanntly in Sjogren's syndrome and radiotherapy receiving individuals for head and neck cancers. The studies shows that prevalence increases with age and it is more in postmenopausal women (10.3-33.7%) compared to men (9.7-25.8%). It is important to note that multidimentional factors are associated with xerostomia.[6] Drug induced xerostomia occurs as a result of interference in signal transmission of signals at the parasympathetic neuro effector junctions, causing the depression of the autonomic nervous system. The salivary glands are not affected by therapeutic doses of medications and any damage is reversible with discontinuation use of drugs.[3]

Xerostomia may be caused by systemic diseases such as Alzheimer's disease, depression, diabetes. Infections caused by hepatitis C virus (HCV) or human immunodeficiency virus (HIV), sarcoidosis, lymphoma or graft vs host disease,

malnutrition, burning mouth syndrome, head and neck radiotherapy, chemotherapy or bone marrow transplantation.[6]

NEUROLOGICAL CONTROL OF SALIVARY SECRETION

The autonomic nervous system plays an important role in salivary gland secretion. Acetylcholine agonists act on parasympathetic and muscarinic receptors of those exocrine glands inducing high electrolyte containing salivary secretion, whereas sympathetic stimulation produces the protein component of saliva. Thus, parasympathetic stimulation generates abundant saliva with low protein concentration and sympathetic stimulation produces little saliva with high protein concentration and viscosity. Physiologically, a three component reflex arch regulating salivary gland secretion including afferent receptors and nerves that carry impulses created by taste and mastication activities, a central connection and processing nucleus (salivation center) and an efferent reflex arm constituted by parasympathetic and sympathetic nerves bundles separately, but in coordination, innervate the salivary gland blood vessels and acini. The afferent nerves carry impulses from the periphery to the salivation center in the medulla oblongata, which in turn directs signals to the efferent part of the reflex arch leading to salivation.[7]
Management includes identification of the underlying cause. It is based upon the cause and severity of salivary gland damage. Dry mouth can be minimized by various modalites listed below

ELECTRO-STIMULATION

Neuro-electro-stimulation of salivary glands overtakes a relevant role in therapeutic stimulation of salivation among patients requiring long term therapy. Intra-oral electro-stimulators offer a new non pharmacological method for the treatment of oral dryness. The probe is applied to the intraoral mucosal surfaces by the user between the dorsum of the tongue and the palate for few minutes each day and a stimulating signal is delivered to sensitive neurons of the mouth to induce salivation.It was not massively used due to its large size, high price which resulted in development of salivary neuro electrostimulators, it is a removable intraoral appliance produced for individual patients by using their teeth pattern molds. It has a horseshoe-like shape and fits on the lower dentition, designed such that it is easy to insert and can be removed by the patient, electronic components embedded within the appliance. The miniaturized electronic stimulator is mounted in a removable intraoral appliance controlled and activated by a remote. This remote control permits the patient to communicate with the device and modify its functions.This device significantly reduced dryness of the mouth during application and up to 10 min after its removal.[8]

IMPLANT SUPPORTED ELECTRO-STIMULATING DEVICE

Electrostimulation with implanted devices is not a new concept, and is in use or under investigation for a variety of other conditions, such as the treatment of pain, deafness, bone healing, cardiac arrhythmia (pacemakers), respiratory malfunction.[9] Some patients may require frequent or constant stimulation of the salivary glands. Therefore, a miniature neuro electrostimulating device permanently implanted into the oral cavity was developed. Use of this dental implant based neuro electrostimulator avoids the inconvenience associated with the repeated application and removal of a splint-based stimulator. The miniaturized electrostimulator was packaged in a device that has the dimensions and shape of a molar tooth. This device was mounted on a commercially available osteointegrated implant. A wetness sensor has been embedded into the device to detect changes in moisture or dryness. This implant supported electrostimulating device has been developed to generate continuous or frequent stimuli in the oral cavity without interfering with regular oral functions. The osteointegrated implant is

positioned in the region of the lower third molar that is wisdom tooth to ensure close proximity to the lingual nerve that carries both afferent and efferent salivary impulses and to avoid interference with normal oral function. The surgery is done by transmucosal exposure of mandibular bone followed by preparation of implant bed and insertion of dental root implant and the posterior location of the device ensures that there are no aesthetic concerns. It would be expected that electrostimulation could become the most convenient and safe means to treat xerostomia.[8]

TRANSCUTANEOUS ELECTRIC NERVE STIMULATION (TENS)

Transcutaneous electric nerve stimulation is another useful method of salivary stimulation. TENS in Sjogren's syndrome showed a significant response to electrical stimulation, with few side effects like twitching of facial musculature and anesthesia of the facial skin.

Salivary flow rate was increased immediately after TENS. Although the exact mechanism was not clear. There was an increased salivary flow rate with basic settings of TENS 50 Hz frequency and 250 ms pulse rate.[10] In a study by Hargitai et al electrical stimulation in healthy adults was done by placing TENS electrode pads externally on the skin overlying the parotid glands, 3/4 of participated individuals showed increased parotid salivary flow.[11] Strietzel et al reported that electrostimulation may significantly decrease the sensory dryness leading to beneficial effect.[12] Thus TENS can be considered as non pharmacological approach to improve salivation in xerostomia patients.

LOW-LEVEL LASER THERAPY

Low-level laser treatment (LLLT) is quick safe, non invasive painless therapy it can intensify cell metabolism and it can improve salivary flow and regeneration of salivary duct epithelial cells. Very low-voltage electrical stimulation has also been trialled in patients with salivary gland hyposalivation. Laser light from a pulsed Ga-As laser operating at 904 nm was bilaterally applied on each salivary gland area extraorally on the submandibular and paratid gland areas and intraorally on the sublingual gland area. The exposure time was 120 sec per daily treatment during 10 consecutive days. Low-level laser therapy could significantly enhance salivary secretion and improve antimicrobial characteristics of secreted saliva increased level of secretory immunoglobulin A(sIgA) was seen. Furthermore, low-level laser therapy could improve salivary flow and regeneration of salivary duct epithelial cells.

The low-level laser therapy has been extensively used as a new, non-pharmaceutical intervention and advantageous tool for reduction of xerostomia and improve the quality of life of patient.[13]

ACUPUNCTURE

Acupuncture as a treatment for dry mouth was first reported by the Western medical literature in 1981. Patients with xerostomia due to radiation therapy for head and neck cancer have shown increased salivary flow rates after acupuncture treatment. The possible mechanism of action of acupuncture suggests that, it increases the release of neuropeptides and stimulates the autonomic nervous system, enhancing salivary secretion with xerostomia. Radio immunoassay analysis has been used to examine xerostomia patients and has determined that acupuncture significantly increases both vasoactive intestinal polypeptide and calcitonin generelated peptide in their saliva. Acupuncture has also been shown to increase blood flow to the skin overlying the parotid gland. Using laser Doppler flowmetry, they discovered that blood flow to the skin overlying the parotid gland increased significantly both during and after acupuncture. In recent years, an acupuncture treatment protocol for xerostomia has been developed that involves fewer acupuncture points and a significant reduction in the number of treatment sessions. Three points were needled on each ear Shenmen to calm the

mind, reduce inflammation and hypersensitivity and to support other auricular points, point zero designed to bring about homeostasis, and Salivary gland 2/prime. In addition, an extra point was needled bilaterally at the radial end of the distal phalangeal crease of the index finger.Patients were usually treated once a week for four to five weeks followed by two or three biweekly sessions, each treatment session lasting 45-50 minutes. Salivary flow often improved during the first visit and the duration of improvement increased with each subsequent visit. Hence, acupuncture could play a significant role in enhancing the quality of life of individuals suffering from xerostomia.[14,15]

GENE THERAPY

Gene therapies were developed to treat inherited genetic deficiencies by delivering genetically engineered genes in viral or non viral vectors into the body to replace the defective gene and its product.[16] Gene transfer may be potentially useful for treating inherited single-gene deficiency disorders and malignancies refractory to other therapies, as well as repairing radiated salivary glands. Baum et al attempted for first clinical trial in human and area of significant progress was seen in radiation damage repair, the results from this study demonstrated that AdhAQP1 improved salivary flow rates in targeted parotid glands and led to reduction in subjective complaints.[17]

STEM CELL THERAPY

Stem cells are cells capable of self renewal differentiation into all lineages of an organ and are useful in regenerating tissues. They have inherent capacity to migrate to injured tissue. Stem cells in salivary gland are responsible for regeneration of the damaged glands. In irradiation, the stem cell population of salivary glands is destroyed. So replacing these disrupted stem cells with new stem cells, thereby regenerating the Salivary Gland Epithelial Cells (SGEC) and protecting the gland. Adipose stem cells appear to be more attractive option with potential to cure and protect patient from xerostomia. Stem cells play a vital role in the response of salivary glands to radiotherapy as they are essential in tissue repair.[18]

BIOLOGICAL THERAPY

The primary drug of the current biological agents being used in the treatment of SS-induced hyposalivation is CD20-targeting rituximab. CD20 is a B cell marker present on the cell surface from late pro-B-cells to memory B cells. Chimeric anti-CD20 antibodies deplete B cells, which is expected to be beneficial in B cell mediated autoimmune diseases, such as SS. Recently the current therapeutic regimens are the two initial infusions followed by repeated infusions at intervals of 6 months to 3 years. B cells probably play important roles for various aspects of SS, but better understanding of pathomechanisms will allow more directed therapies.[19]

Xerostomia remains one of the most common sequelae of head and neck cancer therapy because of excessive radiation to the salivary glands, radiotherapy induces apoptosis of the acinar glands leading to decreased salivary production. The most radiosensitive salivary gland is parotid gland followed by submandibular, sublingual and minor salivary glands.

Intensity Modulated Radiotherapy (IMRT)

Itis an advanced form of 3D-CRT, it allows to deliver a high radiation dose to the tumor, with improved target conformality and surrounding healthy tissue sparing. This technique uses a multi-leaf collimator (MLC) comprising many narrow, mobile lead leaves, to shape the radiation beam and produce convexities in the dose distribution. IMRT will therefore define concave and convex shapes thus allowing high-dose treatment of tumour sites but avoidance of adjacent non target normal tissues. IMRT has the potential to allow dose escalation to the tumour which will increase cell kill and improve recurrence, cure rates and also reduce xerostomia.[20]

Proton therapy

It is a promising and emerging modality of radiation therapy for patients with head and neck cancers, because of the potential to improve organ sparing and safely escalate doses of radiation delivered.[21] Intensity modulated radiation therapy, novel radiotherapy techniques such as proton therapy can minimize radiation exposure of salivary glands, sparing salivary function and improving xerostomia.

SALIVARY GLAND TRANSFER

Three major salivary glands are located in the radiation field when HNC patients receive conventional RT and radiation damage to these glands is permanent. The basic feature of submandibular gland transfer for the prevention of xerostomia is the transfer of the submandibular gland to the submental area. A stopper is set in the submental area, and only approximately 5% of the total radiation dose (30–32.5Gy) is received by the submandibular gland; thus, the submandibular gland remains free from damage.Therefore submandibular gland transfer is an effective method for preventing xerostomia after RT.[22]

PARASYMPATHOMIMETIC DRUGS

They stimulate the part of the autonomic nervous system responsible for the secretion of saliva from the salivary glands. In 1986, an initial report of use of pilocarpine for relief of xerostomia and increase of salivation in subjects with salivary gland dysfunction was noted.[19]

Pilocarpine

It is a cholinergic parasympathomimetic agent acting primarily as a non-selective muscarinic agonist, it also possesses mild beta-adrenergic stimulating properties. Pilocarpine increases salivary secretion by direct stimulation of salivary muscarinic receptors on the acinar cell surface. The increased secretion leads to moisture of the oral mucosa and reduction of dryness in the mouth. The standard initial dose is 5 mg, 3 times a day. [23]

Slow-release preparations of pilocarpine have been developed to minimize side effects and prolong the drug's duration of action. Nanoparticles loaded with pilocarpine is being investigated as a new mode of drug delivery.[24]

Cevimeline

It is another parasympathomimetic agonist that has been used for the treatment of oral dryness in patients with Sjogren's syndrome. Cevimeline is a cholinergic agonist that binds with M3 muscarinic receptors on salivary and other exocrine gland.[19] The combined use of anetholetrithione and pilocarpine has shown to be effective, as anetholetrithione increases the number of cell surface receptors on salivary acinar cells, and pilocarpine stimulates the receptors.[25]

Human interferon-alpha

It has significantly increased salivary secretion in SS patients. Oral administration of 150 IU interferon-alpha 3 times a day for patients with primary SS improved saliva production and relieved symptoms of xerostomia.[26]

Nizatidine

It is an H2 receptor antagonist with the ability to inhibit acetylcholinesterase, resulting in an increased availability of acetylcholine. Kasama et al conducted small controlled, open-label trial in subjects with SS and demonstrated improvement in stimulated salivary output and complaints of dry mouth. Further, more definitive, trials are required.[27]

Alpha-tocopherol

Alpha tocopherol(400 IU daily) supplementation during and after radiation treatment has been found to lessen the reduction in resting whole saliva flow but additional studies are warranted to establish its benefit.[28]

HYPNOSIS

It has been suggested to be of some benefit in improving salivary gland function, but more datais required to confirm ts role in the treatment of xerostomia.[29]

HYPERBARIC OXYGEN

Hyperbaric oxygen when used immediately following radiotherapy, that potentially enhances neo-angiogenesis and mobilisation of stem cells from bone marrow, it has been found to improve xerostomia associated quality of life, however still there is a need for more robust studies.[30]

TOPICAL PREPARATIONS

Commercial saliva substitutes are most frequently applied for relieving the sensation of dry mouth, majority are based upon carboxymethylcellose, hydroxyethyl cellulose. Toothpastes supposedly designed for the treatment of dry mouth are sometimes used as part of a mouthcare system with gels and mouthwashes to improve xerostomia and symptoms allied to oral dryness but do not improve salivary gland function. Gums of various types containing xylitol/sorbitol, can reduce symptoms of xerostomia.[19]

CONCLUSION

Saliva is essential for the maintenance of oral health.There are several etiological factors that may reduce the salivary flow causing xerostomia or dry mouth.Although management of xerostomia is difficult,several treatment modalities have been attempted.The current trends as mentioned in this review would be beneficial in the reduction of symptoms associated with xerostomia and also improve patients quality of life.

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