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Review Article

Dentistry Section

Latest Advancement in the Management of Xerostomia: A Review

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ABSTRACT

Xerostomia, also known as dry mouth, is a subjective sensation arising due to the reduced salivary flow. The dry mouth interferes with normal oral functions such as swallowing, chewing and speech. An increase in the incidence of dental caries and oral infections that may impact the oral health is also seen. The aetiology of dry mouth may be due to systemic diseases, drugs or by radiation to the head and neck, the causes hence being multifactorial. The prevalence of dry mouth is commonly seen in nearly half of the elderly population and one fifth of the younger individuals. Salivary substitutes are used to manage xerostomia. However, for long-standing xerostomia, a lot of potential systemic therapies exist. Oral health care providers are now making significant contributions to the diagnosis and are aware of the latest trends in the management of xerostomia. This review aimed to illustrate the current trends in the management of xerostomia.

Keywords: Dry mouth, Hyposalivation, Xerogenic drugs

INTRODUCTION

Saliva performs a vital role in preserving and maintaining the health of the oral cavity. However, sometimes it is taken for granted until its quality or quantity decreases [1]. Xerostomia is defined as a subjective complaint of dry mouth [2]. The prevalence of xerostomia is seen in 5.5% to 46% of the general population, particularly increasing with increase in age [3]. A possible reason for the elderly individuals is taking several xerogenic drugs (antiparkinsonian, antipsychotics, etc.,) due to prevailing chronic conditions thus, creating an overall decrease in the unstimulated Salivary Flow Rate (SFR) [3].

The diagnosis and treatment of xerostomia is often challenging for dentists as it can have potentially devastating effects in the oral cavity. Detection at the early stage and comprehensive care along with collaboration with physicians may prevent xerostomia. The aim of this review is to explore the current advancements in the management of patients affected by xerostomia.

LITERATURE SEARCH

This literature review was done by thorough search from published peer reviewed journals and articles from the year 2001 to 2019 were scrutinised. The search was conducted using the PubMed database. The following terms were utilised to find the relevant information "Xerostomia", "Management of dry mouth", "hyposalivation". A total of 30 references from journals were finalised and were considered relevant to "Latest Advances in the Management of Xerostomia". This study was conducted at TPCT's Terna Dental College from January 2021 up to April 2021.

AETIOLOGY OF XEROSTOMIA

Several oral and systemic causes such as diabetes mellitus, thyroid disease, Human immunodeficiency virus, hepatitis C, rheumatoid arthritis, systemic lupus erythematosus, Primary biliary cirrhosis, scleroderma, granulomatous reaction, tuberculosis, ectodermal dysplasia, candidiasis [4] contribute to the changes in the flow and composition of saliva. Drug induced Xerostomia is a common aetiologic factor. The common xerogenic drugs include antiparkinsonian medications; antidepressant medications, including selective serotonin reuptake inhibitors; sedative agents, including benzodiazepines; antihistamines, including first and second generation agents; antihypertensive medications, including angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, α-agonists, and beta blockers; anti-HIV agents; opioids; cytotoxic agents such as interferon, ribavirin [5,6].

In addition, radiation of the head and neck most commonly leads to hyposalivation and xerostomia. Exposure to 60 Gray (Gy) or higher radiation results in destruction and apoptosis of salivary glands [5]. Heavy snoring along with temporary factors such as upper respiratory tract infections (viral and bacterial), mouth breathing, and dehydration can also result in xerostomia [7].

CLINICAL MANIFESTATIONS

The clinical features of xerostomia incorporate oral manifestations as well as functional changes. The oral manifestations such as pale and dry cracked oral mucosa that is highly prone to gingivitis and bleeding is observed. They encounter problems such as dysphagia, difficulty in chewing, speaking, and burning sensation in the oral mucosa. Oral candidiasis is also observed. The lack of saliva causes glossodynia and periodontal diseases namely gingivitis, accompanied with halitosis [Table/Fig-1]. An increased risk of developing dental caries is experienced in patients with Xerostomia. Functional changes subsume an altered taste sensation. The normal watery free flowing saliva is replaced by a stringy and foamy consistency of saliva that produces a discomfort to the denture wearers [Table/Fig-1]. The filiform papilla on the dorsal surface of the tongue appears fissured and cobblestone like [8].

Oral manifestations	Functional changes
Increased risk of dental caries	Altered taste sensation
Dysphagia, difficulty in chewing and speaking	Discomfort in wearing dentures
Gingivitis, periodontitis	Cobblestone-like filiform papilla
Oral candidiasis	Thin, pale, cracked oral cavity
Angular cheilitis	
Halitosis	
Glossodynia	
Burning sensation of the oral mucosa	

[Table/Fig-1]: Clinical manifestations [8].

DIAGNOSIS OF XEROSTOMIA

Pai S et al., developed a questionnaire scale which was visual wherein patients were asked to score the severity of their Xerostomia [9].

Objective diagnosis can be done by calculating the SFRs which is done either 2 hours after a meal or 5 minutes after fasting overnight [3] or by Sialometric tests. The range for normal stimulated SFR is 1.5-2.0 mL/min whereas the range for unstimulated SFR is 0.3 to 0.4 mL/min [3]. In case of salivary gland disorders, various imaging systems like sialography, Ultrasonography (USG), Fine-Needle Aspiration Cytology (FNAC) can be used. The computed tomography scan, magnetic resonance imaging of the salivary glands can also prove to be of great significance [10]. Similarly, salivary gland biopsy can also be used to determine the underlying cause [10].

NEUROLOGICAL CONTROL OF SALIVARY SECRETION

The autonomic nervous system is of utmost importance in salivary gland secretion. The parasympathetic and muscarinic receptors of exocrine glands are acted on by cholenergic agonists that induce saliva containing high electrolyte, while the sympathetic stimulation generates the protein component of saliva [11]. Stimulation of sympathetic neurons causes vasoconstriction that produces a small quantity of saliva from the submandibular gland (rich in organic material) whereas stimulation of the parasympathetic results in vasodilation that leads to copious watery saliva secretion (low in organic material) [11]. Application of electric stimulation to one or three components of salivary reflex arc should theoretically rise the saliva production and eventually decrease the effects of xerostomia. Recent advancements in the salivary gland pacemakers are the Salitron system, Saliwell GenNarino, SaliPen, and Saliwell Crown which have been later elaborated [11].

TREATMENT STRATEGIES

Electro Stimulation

In the recent years, the application of extraoral Transcutaneous Electric Nerve Stimulation (TENS) over the parotid gland was observed to enhance the production of saliva in healthy individuals and in patients affected by Xerostomia induced by radiation, claiming that auriculotemporal nerve (supplies the secretomotor drive over the parotid) is directly stimulated by TENS [12]. On the other hand intraorally, the salivary pace makers are illustrious and broadly classified into three generations of electro stimulating devices.

The first-generation device (Salitron) consists of a probe which is placed on the intramucosal surfaces between the dorsum of the tongue and palate every day for a few minutes and this creates a signal directed towards sensitive neurons to stimulate saliva production [12]. This device has merits such as immediate results and long term effect with subjective improvement of the dry mouth condition. However, the drawbacks were the large size, high price of the device and it greatly lacked in user friendlessness which contributed to the limited use of the first-generation device leading to the development of second generation electro stimulator [12].

In the second generation, the devices (GenNarino Saliwell) were in great similarity to a mouth guard which is used in temporomandibular joint disorders and bruxism. It is customised for a particular patient by using teeth pattern molds, a horseshoe shape that fits on the lower dentition. The appliance has the electronic components fitted inside for the safety and comfort of patients. A remote control is used by the patient to communicate with the device and change the function according to their requirements. A study conducted revealed that the device was tolerated well by patients with no adverse effects [13].

Dental Implant Supported Third Generation Electro Simulator

Lastly, dental implant based third generation intra oral device (Saliwell Crown), usually used in patients that require repeated stimulation of the salivary gland. The osteointegrated implant is situated in the mandibular third molar region in close proximity to the lingual nerve that directs afferent and efferent impulses and avoids repeated application and hindrance to the normal oral function which is a prominent advantage. The surgery is relatively simple, and the posterior location prevents aesthetic concerns [12]. A clinical study revealed the long-term effect of the third generation electro stimulation is still under trial, and if they turn to be promising, it would be the most remarkable, convenient, efficient and safe method to treat dry mouth [13].

Low-Level Laser Therapy (LLLT)

Low-Level Laser Treatment (LLLT) is a rapid, non invasive, safe painless therapy which can intensify metabolism of cell and promote salivary flow along with regeneration of epithelial cells of salivary glands [12]. Extremely low voltage electrical stimulation is trialed in individuals with salivary gland hyposalivation. Laser light (out-of a pulsed Ga-As at 904 nm) was adjusted bilaterally on each salivary gland area (submandibular and parotid gland areas extra orally; sublingual gland areas intraorally). During the 10 successive days, the exposure time has to be 120 seconds daily. This treatment significantly improves the salivary secretion and enhances secreted salivas' antimicrobial characteristics (increase in level of secretory immunoglobulin A) [14].

The LLLT has been widely used as a novel, non pharmaceutical intervention and is a beneficial tool for alleviating xerostomia and enhancing the quality of life of patients [14]. LLLT utilises light energy in form of photons to generate cellular responses in cell [15]. Lopes CO et al., and Simões A et al., have shown that LLLT decreased Xerostomia and increased stimulated SFR [16,17].

Acupuncture

Due to the limitations of the conventional therapies, one of most popular Complementary and Alternative Medicine (CAM) therapy used in the treatment of xerostomia is acupuncture [18]. Acupuncture simply means to puncture using a needle [19]. The treatment involves inserting very thin solid needles into areas of interest and later gently manipulating by hands or with light stimulation [19]. The mechanism of action of acupuncture posits that, it intensifies the discharge of neuropeptides and spurs the autonomic nervous system, promoting salivary secretion in xerostomia [14]. These released neuropeptides contain antiinflammatory and trophic effect in the salivary gland and eventually increase the blood flow in the acini [19].

With the help of laser doppler flowmetry, they observed an increased blood flow to the skin over the parotid gland both during and post acupuncture therapy [14]. The treatment protocol in xerostomia patients involves acupuncture points in order to reduce the treatment sessions substantially [14]. To lessen the inflammation, hypersensitivity; and relax the mind, three points were needled on both ear Shenmen. A point zero for homeostasis was described for strengthening other auricular points and salivary gland 2/prime. An additional point was needled on either sides at the radial end of the distal phalangeal crease on the index finger. The treatment is provided every week and lasts for four to five weeks following two-three biweekly appointments, lasting for 45-50 minutes. The salivary flow usually ameliorated during the first follow-up visit and patients recuperated with subsequent visits [14].

Gene Therapy

The delivery of genetically engineered genes in viral/non viral vectors to replace the abnormal gene and its product in the body is made plausible by gene therapy [14]. A significant area of progress was observed in radiation damage repair, from this study conducted by Baum BJ wherein the results indicated that AdhAQP1 (experimental drug) enhanced the SFRs in targeted parotid glands and eventually led to reduced subjective complains [20].

Stem Cell Therapy

Stem cells are cells that are capable of renewing themselves into lineages of an organ and are beneficial in restoring tissues [14]. They

have the capacity to regenerate the injured glands. Khalili S et al., concluded that Mesenchymal Stem Cells (MSCs) when injected intravenously, prevented the loss of salivary flow and decreased lymphocytic infiltration of the salivary glands [21]. Adipose stem cells manifest to be a viable option with the capability to safeguard against and treat xerostomia [14].

In case of radiation induced salivary gland dysfunction and xerostomia, utilising a local injection of MSC's directly in the submandibular gland disclosed a compelling increase in saliva secretion (41%) compared to the saline-treated control, with increase weight of glands [22]. Xu J et al., thereafter investigated the effects of injecting intravenously bone marrow MSCs in twenty four patients with Sjogren's Syndrome (SS), including eleven with xerostomia. All patients well adapted to the MSCs with no complications both during and after MSC infusion. The unstimulated salivary flow improved considerably after two weeks of infusion and eventually increased by two-fold in the subsequent month with the continued rise in the succeeding follow-up visits [23]. Stem cell is imperative when salivary glands are exposed to radiotherapy as they are indispensable for mending tissues [24].

Pharmacological Therapies

A part of the autonomic nervous system is stimulated by the parasympathomimetic drugs which are responsible for generating saliva from the salivary glands. A report posited the use of pilocarpine for mitigating xerostomia and increasing salivation in patients with salivary gland dysfunction [25].

Pilocarpine: It fundamentally is a cholinergic parasympathomimetic agent functioning essentially as a non selective muscarinic agonist. It also exhibits mild beta-adregenic stimulating properties [14]. This drug increases salivation by directly triggering salivary muscarinic receptors on the acinar cell surface. This increased saliva production results in a moist oral mucosa and a decreased dry mouth. The accepted dose initially is 5 mg, thrice a day [26].

Cevimeline: Another parasympathomimetic agonist that treats oral dryness inpatients suffering from SS. It binds with M3 muscarinic receptors on other exocrine and salivary gland [25]. When combined with anetholetrithione and pilocarpine, this agent has shown favourable results as the receptors are stimulated by pilocarpine and the number of cell surface receptors on salivary acinar cells is increased by anetholetrithione [14].

Human interferon-alpha: The standard oral administration of 150 IU of interferon-alpha thrice a day for patients with primary SS relieves symptoms of xerostomia and significantly improves saliva secretion [27].

Alpha-tocopherol: The daily supplementation of alpha-tocopherol (400 IU) during and after radiation therapy has substantially proved to reduce the intensity of resting whole saliva flow. However, further research requires validating this claim to establish its advantage [28].

Nizatidine: This drug is an H2 receptor with the potential to restrict acetylcholinesterase leading to an increased accessibility of acetylcholine. A small controlled, open-labeled trial was led by Kasama T et al., wherein participants with SS demonstrated excellent improvement in stimulated salivary output and complaints of oral dryness [22].

Hypnosis

Although there is some benefit of hypnotic therapy in treatment of salivary flow, there are no evident study trials to conform its role in the treatment of xerostomia [14].

Hyperbaric Oxygen

The most common complain of xerostomia is observed in patients receiving irradiation for tumours involving the oral cavity mainly salivary glands, because they are in the field and are more likely to develop xerostomia as compared to the cancers of the head and neck where no major and minor salivary glands are irradiated. Due to poorly tolerated pharmacological therapies in these patients and the complementary strategies like acupuncture having little evidence in the treatment of xerostomia. Hyperbaric Oxygen Therapy (HBT) is one such strategy that is recommended for the treatment of xerostomia [29].

The application of hyperbaric oxygen therapy following irradiation enhances neo-angiogenesis and aids in the mobility of stem cells from bone marrow. Thus, proving to improve and relieve xerostomia. However, robust studies are yet to provide elaborate evidence of its use in the treatment of xerostomia [14]. A summary of all the treatment modalities have been given in [Table/Fig-2] [6,12,14,19,30].

Treatment modality	Treatment strategy
Electro stimulation	Neuroelectro stimulation is employed to generate saliva [12]
Low-level laser therapy	Modulating numerous metabolic, photophysical and biochemical processes that convert laser light to functioning energy for the cell [6]
Acupuncture	Releases neuropetides and stimulates autonomic nervous system increasing the saliva secretion [19]
Gene therapy	Studies display propitious results of aquaporin-1 enhancing Salivary Flow Rate [14]
Stem cell therapy	Restore and regenerate the acinar cells thereby increase the saliva flow rates [30]
Pharmacological drugs	Pilocarpine, Cevimeline, Alpha-tocopherol, Nizatidine and human interferon-alpha aid in reliving dry mouth symptoms [14]
Hypnosis and hyperbaric oxygen	Evidence based studies are yet to be provided to strengthen the claims [14]

[Table/Fig-2]: Treatment modalities [6,12,14,19,30].

CONCLUSION(S)

Saliva is an element that is extremely necessary in order to maintain good oral hygiene and health of the oral cavity. The causes of xerostomia are abundant. Even though the management of xerostomia is quite difficult, there are several upcoming strategies and new treatment modalities that are mentioned in this review that favours in counteracting xerostomia. The latest advances in the treatment of xerostomia that are enumerated in this review would be advantageous in decreasing the symptoms and further worsening of xerostomia and help in improving the quality of life of patient suffering from xerostomia.

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