Review Article
Available online at www.ijpras.com

ISSN 2277-3657

Volume 4, Issue 3 (2015):35-47

International Journal of Pharmaceutical Research & Allied Sciences

Xerostomia: Post Radiation Management Strategies

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Subject: Pharmacology

Abstract

Xerostomia is clinically denoted by feeling of dryness in the mouth due to decreased production of saliva. Prevalence of this condition is about 20% in the general population with highest rate of incidence in females and elderly people. Xerostomia (feeling of dryness) can impair the patient's ability of speaking, swallowing and chewing, but the extent of dysfunction is dependent on the dose of radiation and the size of irradiated tissues. Average radiation dose of 10 to 15 Grays is associated with minimum dysfunction of salivary glands. But when the radiation dose is greater than 40 Gray, then maximal dysfunction (approx 75%) is observed in the salivary glands which are radiosensitive in nature. When radiotherapy induced in xerostomia, patients they are at highest risk of developing oral infections like gingivitis, periodontitis, viral and as well as fungal infections. Xerostomia can be managed by various means such as intensity modified radiation therapy (IMRT), transplantation of salivary glands, sialagogues (saliva stimulants), oral hygiene and by different salivary substitutes or artificial saliva. This brief study give explanation about different management approaches for radiotherapy induced xerostomia.

Keywords: *Xerostomia, Xerostomia management, salivary substitutes, artificial saliva*

1. Introduction

In head and neck treatment, radiotherapy is generally used as definitive treatment either alone or concomitantly with surgery and chemotherapy. One of the most alarming side effects associated with radiation therapy is mouth dryness[1, 2]. The term dry mouth was first time described by bartley as medical symptom in 1868. According to him, clinical manifestation of this condition was based on dryness of buccal mucosa and abolition of salivary ducts[3]. After 21 years, In 1889, Hutchinson was the person, who gave the name 'xerostomia' to this condition[4]. Xerostomia is usually defined as subjective feeling of dryness in the mouth [5]due to the reason of having viscous, decreased or lack of salivary secretions[[6, 7]. According to the National Institute of Dental and Craniofacial Research-National Institutes of Health (NIDCR), it is a medical condition in which patient is unable to moist his mouth normally due to absence of sufficient saliva[8]. Parotid, submandibular, sublingual and some minor salivary glands(lingual, labial, buccal, palatine, glossopalatine) are mainly involved in saliva production which can be unstimulated(resting) and stimulated[9, 10]. Along with other glands, about 60-70% of stimulated saliva is produced mainly by parotid gland(with flow rate 0.2-0.7ml/min) but for the most part of submandibular and sublingual glands and minor salivary glands are involved in unstimulated saliva production(approx 65% with flow rate of >0.1ml/min).While rest of the unstimulated saliva is contributed by parotid gland(20%) and the sublingual gland(7-8%)[11, 12].In healthy person, normal saliva flow is about 500ml-1.5L per day[9, 13]but in xerostomic condition, salivary flow rate is less than 0.1ml/min[14]. Xerostomia may be expected from the hypo functioning of salivary glands in which composition and quantity of saliva is changed[15]. Acinar atrophy and persistent swelling of salivary glands are hallmarks of radiation associated injury(resultant effects of radiation-induced apoptosis and necrosis)[1] that leads to dysfunction of salivary secretions[16]. Xerostomia has a negative effect on

patient's health status [17, 18]because dryness enhances the vulnerability to infection and as a result patient's power of speaking, chewing and swelling will be compromised[19]. Radiation dose of up to 70Gy is usually required in combination with chemotherapy to treat the oral cancer but above 40Gy radiation dose is enough to produce damaging impact on salivary flow rate(amount of saliva production)[20, 21] . For the treatment of all types of HNC, radiation in fractionated doses (2.0Gy/d*5d) are administered up to the total dose of 50-70Gy over 5-7 weeks [9]and severe dysfunction of salivary glands occur when major salivary glands are involved in irradiation field[16]. Salivary glands specially parotid glands are extremely radiosensitive[22]. single radiation dose of 20-40Gy have potential to stop the salivary flow permanently[21]. It is evident from previous studies that each gray is responsible for approximately 4%–5% reduction in the parotid gland output[23, 24]. The total output reduction is highly influenced by radiation field (table 1) [21]. It is documented in Ohrn and colleagues study that RT decreases the saliva flow rate and increasing the chance of oral complications. After evaluating 18 patients, they found that an association is present between alteration of salivary function and frequency of oral complications[25].Xerostomic condition can lead to further complications such as persistent dry mouth, mucosal changes, plaque accumulation, injuries of oral mucosa, halitosis[26], nocturnal oral discomfort, Oropharyngeal burning, Thirst, denture stomatitis[27], Candidiasis[28], oral mucositis, dysphagia[29, 30], enamel erosion, root caries, periodontal diseases[31, 32], Changes in oral microbial flora, decreased dietary intake and change in taste alteration[33, 34]

Table no 1: Radiation field Vs reduction of salivary flow

Radiation field	Reduction % of salivary flow
Bilateral radiotherapy	Upto 80%
Unilateral RT	50-60%
Mantle therapy	30-40%

Table no 2: Delayed complications due to radiotherapy

Complications	Radiation dose	References
Xerostomia	>50Gy	[35]
Osteoradionecrosis (ORN)	≥66Gy	[36]
Radiation fibrosis (RF)	>40Gy/>60Gy	[37]
Trismus	>55Gy	[38]
Stricture and Dysphagia	≥ 50 Gy	[39]
Moderate to severe carotid disease	≥ 50 Gy	[40]
Pituitary-Hypothalamic Dysfunction	30-50Gy	[41]
Thyroid dysfunction	30-70Gy	[42]
Radiation-induced cataracts	>8-10Gy	[43]
Dry eyes	>57Gy	[44]
Non proliferative retinopathy (NPR)	45-55Gy or >55Gy	[45]
Ototoxicity	>50Gy	[46]
Temporal lobe necrosis (TLN)	BED>80Gy	[47]
Brachial plexopathy	43.5 to 60 Gy	[48]

2. Prevalence

In one study, prevalence between 10 and 50% is reported for xerostomia. In general population, its prevalence is about 20% with increased incidence in females (up to 30%) and in elderly (up to 50%)[15, 49, 50].

3. Measurement and Grading of the Xerostomia

It is very necessary to accurately measure the severity of xerostomia. At present, the most important xerostomic measurement parameters are (1) functional imaging of gland activity e.g Plain-Film Radiography[51], ultrasonography[52, 53], Computed Tomography(CT) , magnetic resonance imaging(MRI)[54], Scintigraphy[[55, 56], Conventional sialography[57], MR Sialography[58, 59] (2) Salivary output measurements either directly by collection of whole-mouth saliva (stimulated /unstimulated)[60] or indirectly by salivary gland Scintigraphy[61](3) observer-assessed toxicity grading e.g Common Terminology Criteria for Adverse Events (CTCAE) and Visual Analog Scale (VAS)[62], and (4) patient-reported assessment of the variety of xerostomia-related symptoms e. g xerostomia questionnaires[63, 64].

4. Management of xerostomia

In order to effectively manage the xerostomia (both acute and chronic cases), frequent evaluation and support is essential to the patient's welfare by embracing an individual treatment schedule (contain all contributing factors of whole mouth care) [21].Palliative measures (local and systemic) included in the main focal points of existing managing strategies of xerostomia. Management protocol of xerostomia basically relies on residual secretory propensity of the salivary glands [38]. Salivary output is affected by many predisposing factors such as dose of radiation, degree of dryness and use of concurrent medications[67]. Additionally, various assessment methods of xerostomia have great influence on measuring parameters of salivary output, physicians' evaluation strategy to score xerostomia, and individual 's own assessment scoring[63, 68]. Significantly, clinicians' grading assessments often different from patient assessments [65]. Eventually, the main objective of management intervention should be relief of xerostomic associated symptoms that have a negative impact on individual's quality of life. Therefore, the most efficient intervention for salivary dysfunction is preventive measures of xerostomia[38].

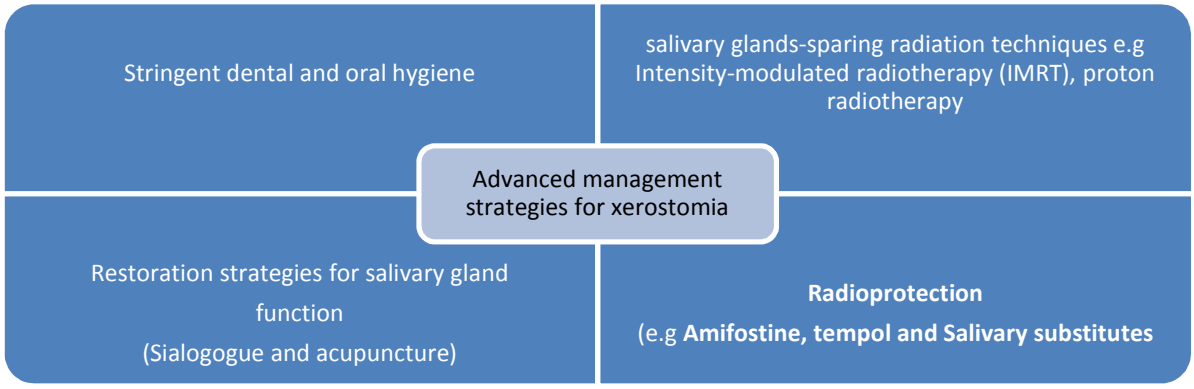
Table no 3: Common Terminology Criteria for Adverse Events (CTCAE) is used to clinically evaluate the severity of xerostomia [65].

Grades	Description	Salivary flow (unstimulated) (ml/min)
One (Mild)	Symptomatic (dry / thick saliva) without significant dietary alteration	>0.2
Two (Moderate)	Symptomatic and significant oral intake alteration (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods)	0.1 to 0.2
Three (Severe)	Symptoms leading to inability to adequately aliment orally; IV fluids, tube feedings, or TPN indicated.	<0.1

Table no 4: Grading of Xerostomia by RTOG system[66]

Grades	Acute (within 90 days from the start of RT)	Chronic (Beyond 90 from the start of RT)
One	Slightly thickened saliva, additional fluids may be required	Slight dryness of the mouth; good response to stimulation
Two	Thick, sticky saliva. Alteration in diet is required	Moderate dryness of the mouth, poor response to stimulation
Three	Inadequate oral nutrition related to salivary gland changes	Complete dryness of the mouth; no response to stimulation
Four	Acute salivary gland necrosis	Fibrosis

Figure no 1: Advanced management strategies for xerostomia[69]



5. Stringent dental and oral hygiene

Oral preventive measure is one of the leading approaches to diminish the radiotherapy induced complications before, during and after the treatment of HNC. Before starting radiation therapy, it is recommended that patients should frequently undergo complete dental checkup that will help to tackle all the possible causes of oral infections and preexistent oral diseases[70, 71] [72].During and after radiotherapy, rigorous oral care is one of the most important element of xerostomia management protocol that decreases the chances of patient's susceptibility to dental caries, plaque and gingivitis[73].

5.1 Salivary glands-sparing radiation techniques

From previous studies, it has been established that risk of xerostomia can be reduced significantly with sparing of at least one of the major salivary glands by keeping mean radiation dose of ≤ 26Gy[74, 75]. Portaluri M et al. has recognized in his dosimetric and clinical evaluation study that patient experienced mild or no subjective feeling of xerostomia by contralateral exposure to parotid gland with mean radiation dose of <30Gy[12]. In 2006, Meirovitz and his colleague found that whole regaining of salivary production can be possible if 33% volume of parotid gland to be exposed contralaterally with mean dose 0f >40Gy[65].In one of the recent study, it has been proved that severe xerostomia can be avoided by keeping either mean radiation dose of 20Gy to one of the parotid gland or 25Gy to both parotid glands [76].

Currently, the most important salivary glands sparing radiotherapy techniques are 3-dimensional conformal RT, intensity-modulated RT (IMRT) and proton RT[76, 77]. These techniques posses improved cytocidal efficiency by allowing increased doses to cancerous tissues while minimum harm to normal tissues [23]. These functions are achieved by intended delivery and thereby having better control on localized tumor hence reducing the RT associated morbidity and enhancing the xerostomia related quality of life[23, 76].

5.2 Restoration strategies to improve residual salivary functions

5.2.1 Sialogogue

The word sialogogue has been derived from the two Greek words sialan (saliva); and agogos (leading) [82]. A sialogogue is characterized by anything (either medicinal agent or a substance) that have potential to stimulate the saliva secretion by promoting the salivary glands function which ultimately leads to enhance the flow of saliva [82, 83]. Saliva stimulant, Sialagogue, Ptysmagogue or Ptyalagogue are other alternative terms used in place of sialogogue [83]. Stimulating effect of sialogogues can be achieved either by Mechanical and gustatory stimulation or by use of medication (table 5)[84]. Salivary secretion can also be induced by electrical stimulation e.g. Salitron that is Intra-oral electronic stimulator of saliva, and by chemical stimulants such as Mouth-Kote (having Mucopolysaccharide Sol with citric acid) and Optimoist (containing citric acid)[85].

Table no 5: Approaches utilized in oral health optimization

Approaches utilized in oral health optimization	References
• Meticulous oral hygiene • Frequent assessment of dental and mucosal health status • Suitable interventions to improve oral complications	[23]
Rigorous oral care include	
• Oral hygiene (plaque control; use of Chlorhexidine, fluoride mouthwash, or fluoride gel daily, High fluoride toothpaste; Complete education of Oral hygiene) • Dentures • Antifungal (Nystatin pastilles, Amphotericin B lozenges, Miconazole gel)	[21]

Table no 6: Benefits against two dimensional radiotherapy

Advanced techniques	Benefits against two dimensional radiotherapy	References
IMRT (intensity modulated radiotherapy)	Precise release of radiation dosage. Accurate distribution of radiation dose to the tumor tissue. Provide better opportunity to spare major salivary glands. Impart significant protection to healthy tissues against cumulated radiation dose. Preserve the sufficient salivary flow rate. Marked diminution of patient- and observer-rated xerostomia.	[78, 79]
Proton radiotherapy	Allowing greater radiation dose distribution in contrast to existing X-ray (photon) RT. Sparing of normal tissues by delivering of minimum dose to them. Considerable declining of radiotherapy induced acute and delayed side effects.	[80, 81]

Table no 7: Sialogogue

Sialogogues				
Mechanical and gustatory stimulants[86]		**Pharmacological stimulants**		
Examples	**Description**	**Drugs**	**Pharmacological class**	**Dose**
Chewing gum (Biotène and Oral Balance products) Other chewgums e.g V6 (Stimorol) and Freedent (Wrigley)	Improve mouth wetting, reduce oral infection by stimulating watery(thin)saliva	Pilocarpine Hc [2, 87]	Cholinergic agonist	Initial recommended dose is 5mg, 3or 4 times /day (usual dose range 15-30mg/day) [88]
Sucking ointment	Helps to stimulate saliva having foamy consistency, mild taste and longer effect.	Cevimeline [89]	Cholinergic agonist having high affinity for M3 receptor	30mg 3 times per day[90]
Taste Menthol Sweet Acid(citric acid)	Aid in producing the mucous saliva Marks the bitter taste of vitamin acid.	Bethanechol	cholinergic–muscarinic agonist	25mg 3 times in a day[250].
		Paramethoxyp-henylpropene [[91]		25mg , 3 times daily
Vitamin C tablets.	Lessen the viscosity of saliva by disrupting the disulfide linkage	physo-stigmine[92]	Cholinesterase inhibitor	1–2mg/ml Locally applied as mouthwashes or in a spray
Bentasil lozenges	Ameliorate the subjective feeling of dryness by its prolonged effect.	**Other stimulants are[93, 94]** Carbachol(parasympatheticomimetic) Anethole trithione(Choleretic) Bromhexine (Mucolytic agent)		

5.2.2 Acupuncture

Acupuncture is usually termed as alternative medicine[95] which utilizes numerous approaches such as infiltration by using thin needle or application of pressure (compelling force), heat or laser light to stimulate the specialized acupuncture points alongside the body skin[96].It is an important element of traditional Chinese medicine but its clinical practice fluctuates from country to country[97].

Prior studies has been demonstrated that acupuncture is considered a comparatively prudent procedure[98]which play pivotal role in stimulating the residual secretory capacity of salivary glands in RT patients of HNC[99]. It has been proved from earlier studies that acupuncture is found to be an efficient technique in promoting the whole stimulated saliva[99, 100]and diminishing the severity of dysphagia and feeling of dryness (xerostomia)[101]. The outcome of acupuncture therapy can persist for at least 6 months which can be further prolonged up to 3 years by inclusion of other acupuncture therapy[99, 100].

5.3 Radioprotection

5.3.1 Amifostine

In order to reduce the severity of xerostomia, Amifostine (aminothiol prodrug) has been found an effective cytoprotectant, which can be used during and after radiotherapy for HNC patients [23]. It can provide direct radioprotection to parotid glands when extensive part of it involved in radiation port because it is scavenger of oxygen radical [23, 102]. It is administered by intravenous route (table 7)[103, 104]. Anné PR et al. has been demonstrated in his study that IV administration of Amifostine is associated with many side effects which can be overcome by its administration through subcutaneous route [104]. After administration, Amifostine is transformed in to its active metabolite (WR-1065) by alkaline phosphatase (a membrane bound enzyme)[105]. This active metabolite is taken by normal cells where it provides protection against harmful effects of radiation and chemotherapy. Normal cells have very high affinity (100 times than tumor cells) toward WR-1065 because of the presence of alkaline phosphatase in adequate amount. Amifostine perform its defending function by eating up free radicals, giving H^+ ion to them and have ability to inactivate the cytotoxic effects of radiation [105].

5.3.2 Tempol

It has been revealed from previous two studies of Vitolo JM et al. and Cotrim AP et al. that stable nitroxide (Tempol) is found to offer radio-protective effect by following mechanisms; imitating the action of superoxide dismutase, oxidizing transition metals and scavenging free radicals[106]. These studies were conducted in animal model (mouse) and provide evidence of the fact that radiation induced salivary gland dysfunction can be considerably reduced by administration of tempol through IV, IP, SC and in topical preparation[106, 107].Later on, Cotrim AP and his colleague has shown in another study that tempol have tendency to provide protection only to salivary gland rather than tumor tissues[108].

5.3.3 Salivary substitutes/ artificial saliva

In order to manage the chronic xerostomia, different salivary substitutes/artificial salivas are commercially available when other stimulants (sialogogue) are failed to induce the saliva flow (residual salivary secretion)[112].The artificial salivas are usually termed as aqueous solution preparation, chiefly comprises of glycoprotein or mucins, salivary enzymes(lysozyme, peroxidase, glucose oxidase) and polymers(carboxymethyl cellulose) that substitute the salivary gland hypofunction in severe xerostomic patients[113-115].The artificial salivas have very close resemblance to natural human saliva in term of their chemical composition and biophysical properties(table)[116].

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Table no 8: Recommended dose of Amifostine

Recommended dose of Amifostine	Frequency	Administration guidelines
200mg/m^2	Once daily	3-minute intravenous (IV) infusion, 15-30 min before starting radiotherapy.

Table no 9: protective agents

Agents	Description	References
Insulin growth factor 1 (IGF-1)	Inhibit radiation induced programmed cell death (apoptosis), and conserve salivary gland function.	[109]
keratinocyte growth factor (KGF)	Restrict the post radiation associated abnormal growth of acinar cells of salivary glands that results in improved hyposalivation effect.	[109, 110]
Botulinum toxin	Reduce radiation induced injuries to submandibular glands.	[111]

Table no 10: Natural saliva Vs artificial saliva[117]

Significant characteristics	Natural saliva	Artificial saliva
Mucoadhesive nature	✓	✓
Lubrication	✓	✓
Shielding/protection	✓	✓
Digestive action	✓	×
Enzymatic action	✓	×

6. Conclusion

In this review we have discussed about Xerostomia. That is clinically denoted by feeling of dryness in the mouth due to decreased production of saliva. Prevalence of this condition is about 20% in the general population with highest rate of incidence in females and elderly people. This review has discussed the different strategies (Stringent dental and oral hygiene, salivary glands-sparing radiation techniques, Sialogogue, acupuncture and Amifostine, tempol and Salivary substitutes) that were utilized to manage the xerostomia after radiotherapy. This study also provides sufficient information to young researcher about grading of xerostomia and several novel radio-protective agents for its management.

"Cite this Article"

A. Tariq, M. Jamshaid, I. Majeed "Xerostomia: Post Radiation Management Strategies" Int. J. of Pharm. Res. & All. Sci. 2015;4(3):35-47

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