ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Management Of Radiation Caries With Biotherapeutic Modifiers: An Overview.

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ABSTRACT

Every year there is an increase in head and neck malignancy patients who are diagnosed all over the world. Radiotherapy is the most preferred treatment choice; however, it leads to many unavoidable side effects. Radiation-related adverse effects have direct and indirect consequences on oral structures, that may be acute or chronic. These adverse effects include mucositis, xerostomia, loss of taste, dental caries, infection, trismus, and osteoradionecrosis. Irradiated patients are often associated with radiation caries which are initially incipient lesions butwhen left untreated, progress rapidly to involve the pulp, as it is rampant in nature. Caries may even affect teeth not in line of radiation leading toloss of existing dentition over a few months if left untreated. Dentists play a pivotal role to prevent this condition by enhancing and reinforcing mineralised tissue by locally altering the biochemistry and biomechanical properties, closely monitoring oral healthcare before, during, and after the initiation of cancer therapy. In the present article, various biotherapeutic modifiers have been classified as direct and indirect methods/agents for a simplified overview. Direct methods include remine ralising agents and lasers where as indirect methods include saliva substitutes, nutraceuticals, acupuncture and stem cell replacement therapy.

Keywords: Biotherapeutic Modifiers, Nutraceuticals, radiation caries management, xerostomia

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ISSN: 0975-8585

INTRODUCTION

Most common treatment choice forhead and neck cancer therapyis radiation which may be administered through either conventional Radiotherapy (RT), Intensity Modulated Radiotherapy (IMRT), chemoradiation (CRT) or brachytherapy. Although the amount the radiation exposure varies depending on the mode of administration however the common side effect the patient must endure is of reduction in the salivary flow(hyposalivation) and change in nature of saliva. Apart from these; other oral complications post radiationis mucositis of soft tissues, changes in nature of saliva like buffering capacity and imbalance of its contents, fibrosis, sensory dysfunctions like loss of taste and altering food palatability, incipient caries which later progress into rampant caries, root caries, periodontal conditions and osteoradionecrosis. [1, 2]The term "radiation caries" is rampant caries following RT to head and neck region. [3] Clinically it is difficult to differentiate radiation caries from non radiation caries, in cases with a higher rate of recurrence.[4]

The National Cancer Institute (NCI) in 2015 defines Biotherapy as "a type of treatment that uses substances made from living organisms to treat disease that occur naturally or made in the laboratory. Some biotherapies stimulate or suppress the immune system to help the body fight cancer while others attack specific cancer cells, which prevent their growth or apoptosis."And since, these biotherapeutic modifiers are mostly natural derivatives they tend to have lower side effects.

DISCUSSION

There is no standard treatment for radiation induced caries, due to the dynamic nature of the condition. Patients undergoing RT are recommended to maintain oral health with regular dental check-ups for early identification of demine ralised incipient lesions and advised to use various biotherapeutic modifiers for prevention &/or to promote remine ralization. The various biotherapeutic modifiers have been classified under direct and indirect categories for a simplified overview of the methods/agents.

I DIRECT METHODS: These include;

1.Remineralising agents: The various agents which have been found to be helpful in remineralising the initial demineralisation have been classified into Natural and Synthetic.

Natural:

Proanthocyanins (PAs):These are plant derived metabolites present in fruits, vegetables, nuts and plant seeds. Their antimicrobial capabilityavoids the changes from reactive oxygen species thus inhibiting action of glycosyltransferases. Studies done by Castellan CSet al[5], Bedran-Russo et al[6] and Macedo GV [7] have suggested that agents with PA and glutaraldehyde are effective in restoring function of demineralized dentin, restore its strength, raise the modulus of elasticity and improve mechanical stability by cross-linkingthe collagen.

They can be advised as a dietary supplement due to their natural antioxidant nature and potential as a free radical scavenger[5]. Plant based formulations are a promising alternative to manage carious lesions in cases where overdose of regularly prescribed agents such as fluoride causes toxicity[6]. However, as very few in vivo studies are present further research is necessary to promote the preventive and restorative ability of Proanthocyanidins on dentin.

Xylitol: Xylitol is a five-carbon sugar polyol found in foods, pharmaceuticals, and products used to maintain oral carebe cause of its anti-caries and anti-inflammatory properties. [8]They are available naturally from vegetables and fruits or aby-product of the glucose metabolic pathway in man and animals.[9] Few studies have evaluated the role of xylitol for the treatment of cancer-related complications like providing relief from radiation-induced xerostomia. Study by Tanzer JM et al has shown the antibacterial effect of Xylitol as it lowers the Mutans Streptococci (MS) count in plaque and saliva. Itcauses cell death as a result of disruption in the energy production processes of MS.[10]

Trachootham D et al[11]studied the partial substitution of glucose with xylitol that's up pressed glycolysis inhibiting proliferation of oral cancer cells. The non-transformed cells and oral squamous cell lines

were treated with xylitol or sorbitol as substitutes for glucose, causing reduced cell proliferation due to less adenosine triphosphate (ATP) generation and phosphofructokinase activity demonstrating that xylitol has an antiproliferative effect. [8]All the studies availableon xylitol so far have not evaluated it as a single-agent used independently to treat xerostomia, therefore it can be considered as a supportive treatment measure for radiation-induced xerostomia to maintain oral hygiene or as a saliva substitute. [11]

Extra Virgin Coconut oil: Oil pulling has its origin from Ayurvedic medicine; a healthcare system practiced in India. In recent times other nations like the United States and Europe have accepted and considered Ayurveda as alternative form of medicine. The process of oil pulling involves rinsing or swishing the mouth with unrefined cold pressed pureedible oil from coconut, sesame, sunflower, or olive to prevent and manage oral conditions like tooth decay, halitosis, xerostomia, gingivitis or periodontitis. Several plant oils are considereddue to their nutritional qualities. [12, 13]

Coconut oil is preferred due to50%of lauric acid content; which imparts the antibacterial and antifungal property and makes it palatable to patients. [14] The mechanism of antibacterial action of cold pressed oil from coconut is due to the capability of medium chain fatty acids to penetrate the bacterial cell wall, rupture cell membranes, leading to the death of the bacteria. Existing literature elicits its potency as an antimicrobial agent against, Staphylococcus aureus, Candida spp, H. pylori, C. albicans, C. kruseiandC. tropicalis. [15]

b) Synthetic:

Fluorides: Fluoride is an important agent in any caries preventive or management program. Small quantities in saliva promote mineral deposition into hard tissues and inhibit enamel demine ralisation and facilitate remineralisation. There are several modes of application, but fluoride delivered in trays is most effective. Fluoride can be administered professionally as varnishes and gels or at home use asprescribed toothpaste, mouth rinses, devices with slow-release of fluoride[16, 17]. If the patient is unable to adapt to home use devices that are complex, brush on fluoridelike varnish can be applied twice a day along with diet modifications. Caries prevention, reversal of hyposalivation and lowering the number of teeth to be extracted is possible with a routine use of home fluoride treatment and dental follow-up over a period of 2-3 years while undergoing radiation. [18]

Commonly recommended topical fluorides used as brush on technique or in a customised tray for radiation caries prevention are: [19]

1. Stannous fluoride(0.4 % gel)– Effective to arrest incipient lesions and progress of root surface caries.
2. Acidulated phosphate fluoride(1.23 % gel) -Effective against root surface caries and erosive demine ralisation.
3.Sodium fluoride (1.23 % gel)- Reduces sensitivity to teeth or gingiva and are effective against erosive demine ralisation.

Casein Phosphopeptide Amorphous Calcium Phosphate (CPP ACP): This product is known by the trade name of GC Tooth Mousse containing protein in the form of casein phosphopeptide (CPP) and a mineral part that is amorphous calcium phosphate (ACP). When applied in the mouth, CPP-ACP binds to teeth, pellicle, plaque, and soft tissue surfaces. Several studies show CPP-ACPF (CPP ACP with Fluoride) paste to increase the buffering capacity of saliva, decrease the demineralization process, and improve re-mineralization. The particles are smaller than 2 nm and can enter dental biofilm increasing the CPP concentration in plaque and act as a carrier for fluoride into dental plaque as it bonds to fluoride. These two agents together increase re-mineralization of the tooth structure and elevate the plaque pH. [20]

Long-term compliance with daily supersaturated rinsing with CPP-ACP by itself or in conjunction with fluoride is protective against caries progress in a high-risk population with xerostomia or any systemic disorders. [21]

Bioactive Glass: Main aetiology of dental caries isBiofilmthat isfirmly attached to tooth surfaces. Sodium fluoride (NaF), chlorhexidine and triclosan (TCS) are the biocides which are considered for use traditionally that inhibit bacteria of the oral cavity. The major shortcoming of currently available products is their limited

capacity to remineralize surface enamel by low concentration of calcium and phosphate ions present in saliva. This led to the research of new materials to provide remineralization such as bio active glass (BAG) which is available in several paste formulations.[22] NovaMin is a bio active glass where the active ingredient is the inorganic chemical calcium sodium phosphosilicate and is used for palliative care for hypersensitivity, gingivitis, bleeding, non-carious lesions, carious lesions, as a tooth remineralizer and tooth whiten ingagent.[23]

Taha A.A et al[24] conducted a study to show Bioactive glass with fluoride when propelled via an air abrasion systemis capable of fluorapatite formation on the demine ralized enamel surface after inactivation of the surface biofilm. In vitro investigations are ongoing showing NovaMinas a better dentifrice with greater effect on remineralization of caries when compared to that of fluoride containing dentifrice in permanent teeth.

Tricalcium Phosphate (TCP): It delivers calcium phosphate as well fluoride hence referred to as a "smart" delivery system for selective delivery of calcium and phosphate ions to the teeth, for enamel surface protection. TCP is a precursor with a structure similar to hydroxyapatite. It is designed for use with a fluoride containing paste or varnish. [25]Tooth surface and subsurface are bathed in functionalized calcium ions in a neutral pH environment unlike calcium phosphate additives which need an acidic pH.[26]Functionalized TCP has very low solubility in water and promotes remineralization with moderate levels of calcium content which are a benefit over products where high concentrations of calcium and fluoride form a complex making fluoride inefficient to fight decay. [27] [28]

2.Lasers:

Lasers have been advocated to be used for both; the preventive and therapeutic purposes against enamel surface demine ralisation.

Preventive modality: Advances in caries diagnosis are necessary for early intervention and management hence lasers were introduced which is an emission of coherent light that are absorbed by tissue receptors to promote biological effects.[29] In the visible region (blue or red light) they are capable of caries detection in enamel and dentin. [30]

The mechanism of action is that visible light creates a photochemical change in the photoreceptors of mitochondria, altering cell metabolism resulting in a transduction effect in other cell components or biomodulation effect [29]. CO_2 Laser gives an accurate diagnosis to treat incipient lesions and avoid loss of healthy tooth structure. [30]

Therapeutic modalitiy: Parameters which alter tissue biology are wavelength, voltage, amount of energy delivered to the tissues, time of exposure and the rate of energy delivered to tissues [29, 31]. Lasers have a high sensitivity and specificity and can be a treatment choice for incipient lesions before they turn into rampant cariesor radiation caries. Er:YAG lasers are known for cavity preparation in primary and permanent teeth with an acceptable temperature rise. [32]Depending on the nature of cancer, rate or recovery and cancer treatment regimens the choice of laser and ideal time of application along with other parameters can be set before laser therapy. Migliorati et al have suggested a safe range of 632 and 830 nm which are known to have beneficial effects on preventing and treating oral mucositis that can prevent further complications like caries and xerostomia. [29]Thus, if utilized well lasers used with suitable parameters can obtain the best bio modulation of tissue reactions.

IIINDIRECT METHODS

1.Oral mucosal lubricants/ Saliva substitutes: Easiest way to manage dry mouthis by maintaining good oral hygiene to promote hydrated oral environment and thus prevent secondary complications like rampant caries. Salivary substitutes and non-medicated oral rinses formed of substances like mucin, carboxymethyl-cellulose, and xanthan gum can be advised to relieve these symptoms. Sialagogues and other drugs to treat xerostomia are pilocarpine, cevimeline, botulinum therapy, amifostine, chewing gum and alpha-tocopherol.[2]Pilocarpine is a cholinergic agonist used for the relief of symptoms and may offer some dental protection but not prescribed often as its adverse effects are sweating, diarrhoea and bronchospasm. [2,33]

2.Nutraceuticals: It is the termformed from a combination of the words ‘‘nutrition’’ and ‘‘pharmaceutical’’ refers to any substance considered to be a food or a food ingredient that provides medical and health benefits.[34]
Following are a few commonly considered nutraceuticals:

Curcumin/turmeric /curcuma longa ($C_{21}H_{20}O_6$): It is a bright yellow plant-derived chemical, from the ginger family Zingiberaceae. Regularly used as a herbal remedy and a spice in several dietary preparations.[35] It is known for its anti-inflammatory and antioxidant activities. Curcumin inhibits the growth of cariogenic pathogens, inhibits their binding hence showing its anticariogenicpotential.[36]Duarte et al.[37] show curcumin as a chemo preventive, chemotherapeutic and chemo sensitizing agent as it restricts growth of cancerouscells. According to the report, curcumin acts through epithelial growth factor receptors to inhibit pathways of cancer cell proliferation, having an anti-apoptotic, extra-cellular matrix degradation and angiogenesis. [37,38]

Green Tea Extracts: It is the product from plant Camellia sinensis, commonly consumed as a beverage. Polyphenols such as catechin (−)-epigallocatechin-3-gallate (EGCG) are the active ingredients with therapeutic potential in oral carcinomaswhere they act through several pathways. It has a known effect on control of salivary Ph, inhibit lactate dehydrogenase and thus reduce acid production after sugar consumption. Consumption of green tea gum helps in remineralization of enamel by resistance to acid. Green tea gums are also known to increase the fluoride content of saliva thereby facilitating remineralization.[38] Mechanism of action is EGCG in the cancer cells down regulates formation of matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF). They inhibit extracellular matrix from destruction and lower rate of angiogenesis. [39]

Basil (Tulsi) leaves: commonly known as “Holy Basil” in English and “Tulsi” in Hindi and Sanskrit, found in the semitropical and tropical regions of the world. Eugenol is its active constituent with many benefits along with caryophyllene and phytoconstituents that are isolated from various parts of the plant, they arepalmitric acid, vallinin, galic acid, Vitamin A, Vitamin C, ursolic acid and carvacrol.[40] Tulsileaf (Ocimum sanctum) extract is an important herb in folklore practices for several ailments and diseases, a wide range of conditions ranging from relatively minor illnesses such as cold or a cough to systemic conditions. Direct protective effect of the Ocimum plant extract on radiation induced liquid peroxidation was demonstrated in a study by Devi PU et al where they concluded a pre-treatment with Ocimumextracts 30 minutes before radiation ; showed a reduced liquid peroxidase levels and suggested that they protect the cell membranes against radiation induced oxidative damage.[41]A study conducted by Karthikeyan K et al showed the chemo preventive effect of Ocimum sanctum in the form of fresh leaf paste on D MBA-induced hamster buccal pouch carcinogenesis, where it was concluded that the orally administered O. sanctum may have the ability to lower the incidence of papillomas and squamous cell carcinomas significantly and prevent the early events of carcinogenesis.[42] It has the ability to inhibit the biofilm formation on the tooth enamel surface by inhibiting the bacterial adherence mechanism and leading to bacterial breakdown thus lowering the predisposition to cariogenic activity.[43]

Aloe Vera gel: Mucositis occurs as a side effect of chemotherapy or radiotherapy on epithelial cells of oral mucosa in head and neck cancer patients due to diminution of the protective and buffering effect of saliva. The mucosa is inflamed and under constant stress with a reddish appearance. [2] Studies that have used Aloe Vera Gel, electrolytes such as carboxymethyl cellulose in spray form and rapeseed oil have shown the capability to improve the symptoms of low salivation post radiotherapy and maintain a pH level in the oral cavity that is less favourable to develop caries. [33,44]

3. Preventive and Therapeutic measures:

Acupuncture: Acupuncture originated in China many centuries ago and made its way in to western medical literature in 1981. It is a form of invasive therapy which involves the insertion of tiny needles at specific points, to prevent or cure diseases and symptoms. [45]Accepted by the World Health Organization (WHO) to treatsymptoms of pain during cancer, it has been reported to provide an immediate analgesic effect like that of codeine and pethidine, when used for a period of two months. The effect was comparable with that achieved using the analgesic steps recommended by WHO. [45]The first to report from a study are Braga FPF

et al,where they investigated the capability of acupuncture treatment to prevent irradiation-induced xerostomia. Resting and stimulated saliva samples were analysed from patients who were subjected to acupuncture therapy compared to those who were not. They were unable to eliminate the oral sequelae of RT completely using acupuncture however; lowered severity of dry mouth post treatment. [46]Acupuncture may not be though used as first line of treatment for patients undergoing radiation, however literature suggests it is preferable to pharmacological agents for pain relief and saliva stimulation as no reported casualties are seen so far with side-effects after its administration.[45, 46]It can be considered a safe form of adjunctive therapy to patients undergoing radiotherapy.

4.Stem cell replacement therapy:

Most common treatment plan for patients so far has always involved radiotherapy, chemotherapy and/or surgery or a combination depending on the staging of tumor and other factors. Following which, patients do survive but with irradiation of non-tumorous tissues around the tumor, most commonly the salivary gland leading to other complications like xerostomia, change in taste, halitosis etc which alters the patient's quality of life.[47]Stem cell therapy has a capability to recover damaged tissues from side effects of radiation, can repair tissues which undergo damage after cytotoxic events.[48] Over the last decade advances in research have been made in stem cell-based therapy for long-term treatment of hyposalivation in post-RT patients. Three stem cell types currently used for transfusion are:

i. Embryonic stem cells
ii.Induced pluripotent stem cells
iii. Adult stem cells.[48]

During later phases of RT, salivary gland stem/progenitor cell population get sterilized where the functionally mature acinar cells deteriorate with no new replacement causing a reduced formation of saliva and hence less secretion. Stem cells are known for self-renewal and can replenish damaged cells.

Pringle S et alin their review hypothesis stated that radiotherapy schedules generally last between 5 and 7 weeks suggesting that stem cells should be transplanted soon after RT, before tissue starts fibrosing which may be deleterious to cell engraftment.[49]

A good number of undamaged salivary gland stem/progenitor cell population remain post therapy that determine the recovery, compensatory responses and re-generative capacity of the gland after irradiation. [49]

Although hyposalivation post radiotherapy is a must to be treated but a better understanding of the mechanism is still needed due to a lack in in-vivo studies.

CONCLUSION

The present review revealed that combating cancer with biotherapeutic modifiers whether as plant-derived dietary compounds, nutraceuticals or routine remineralizing agents used for preventive dentistry are a promising approach. Most of the studies that are reported in this review where natural or synthetic bio modifiers were tested have been found to have a positive effect but it is not entirely safe to say they can be used on patients currently undergoing cancer treatment without further studies to examine the adverse effects associated with the use of such agents independently or in association with other drugs. The main concern before implementing the use of these modifiers is their poor bioavailability and acceptance thus, indicating the need for substantial evidence through clinical trials testing the workability, merits and demerit sand questioning the novelty of these applications independently or as a synergistic therapy to mainstream cancer therapy.

Conflict of interest statement: None

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