

Therapeutic Approach on Oral Mucositis

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Abstract

Oral mucositis is a erythematous ulcerated lesion that causes soreness and tissue damage. The lesion leads to severe pain. It occurs on the comparative of nutrition diet, poor oral hygiene and local and systemic infections. The pathophysiology of the oral mucositis consists of five phases where initiation phase leads to injury to the cell. Which leads to activation of transcripts factors which leads to upregulation of inflammatory cytokines and tissue damage as results in subsequent bacterial colonization and cytokines mediated damages . The final phase involves healing through signalling and epithelium proliferation. Maintaining good oral hygiene reduces the severity of the effect and decreases bacteremia . It can be diagnosed by LLLT low level laser therapy. Also can be treated by growth factors, locally applicable gels immune modulators and hematopoietic agents Based on the development of clinical and scientific knowledge standard treatment plan and further research and analysis is needed for management of mucositis. The severity of oral mucositis also may be controlled by advanced plant based or nano based phytochemicals.

Keywords : *ulcerative lesion, local and systemic infections, mucositis.*

Introduction

Advances in the understanding, prevention and treatment of oral diseases during the past 50 years have led to a significant increase. As the goal of modern dental care is oral health, this cannot always be achieved or maintained. Often, only an arrest of disease progression can be attained, and chronic asymptomatic infections may persist. In addition, chronic or malignant diseases of the mucosa are increasingly common. The mouth has thus become a significant potential source of both infection and inflammation that contributes to the total burden of disease and to overall health and well-being.¹

The oral microbiota is both rich and unique. A similar microbiota does not exist elsewhere. In healthy individuals, viridans group streptococci constitute the majority of the indigenous oral flora. However, the most common bacteria seen are facultative anaerobic streptococci and anaerobic Gram-negative bacilli like Prevotellae and *Fusobacterium* spp., etc . Currently, a significant proportion of Prevotellae isolates worldwide are β -lactamase producers, and β -lactam antibiotics alone are thus ineffective against these organisms. For this reason, metronidazole has been used in combination with penicillin in order to achieve improved efficacy against anaerobes.²

Many antibiotics and synthetic oral hygiene products have diminished clinical efficacy, due to the resistance developed to antibiotics and synthetic chemicals, especially in persons with HIV/AIDS. Synthetic substances also have several adverse effects such as vomiting, diarrhoea and teeth staining . In order to overcome these shortcomings, plants and other natural antibacterial substances are now attracting attention as useful and alternative antimicrobials to be incorporated

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into mouth rinses and toothpastes. Since plants are the sources of more than 25% of prescription and over-the-counter drugs, conventional medicine is increasingly becoming receptive to the use of antimicrobials derived from plants and other natural products. The rise in the use of herbal medicines has renewed interest in the effects of plant extracts to control plaque and other oral diseases. Screening for antimicrobial agents isolated from plants is a feasible approach to the identification of natural compounds with antimicrobial properties against dental pathogens. In fact, compounds that possess antimicrobial activities against oral pathogens are now being isolated from plants traditionally used as oral remedies.³

Oral mucositis is an erythematous ulcerative lesion caused by radiotherapy or chemotherapy. It is characterised by oral erythema, severe pain and can predispose to septicaemia in neutropenic patients.⁴ It affects the quality of the life and nutrition state of the patient who may require hospitalisation, thus increasing health care cost.⁵ Oral complications that arise with chemotherapy or radiation therapy include mucositis, xerostomia, bacterial, fungal or viral infection, osteoradionecrosis, dental caries, loss of taste and other oral complications in oral cavity. Oral mucositis also represents a major nonhematologic complication of cytotoxic chemotherapy and radiotherapy associated with significant morbidity pain, dysgeusia, odynodysphagia, subsequent dehydration and malnutrition.⁶ Several oral toxicities can also compromise the delivery of optimal cancer therapy protocols, like dose reduction or treatment schedule modification may be necessary to allow for resolution of oral lesion⁷. The risk of developing mucosal injury increases with the number of chemotherapy cycles and previous episodes of chemotherapy induced mucositis. Drugs affecting DNA synthesis exhibit more pronounced mycotoxin effects^{8,9}. It has been estimated that there is an increased risk of mucositis development with blooms and continuous infusions compared to prolonged and repetitive administration of lower dose of cytotoxic agents^{10,11}. It may also occur in bone marrow transplantation and receive high dose chemotherapy also for patients receiving radiation therapy for cancer of head and neck region may develop oral mucositis¹². The degree and duration of mucositis in patients treated with radiation therapy are related to radiation source, cumulative dose, dose intensity, volume of radiated mucosa, smoking

, alcohol consumption, oral hygiene¹³⁻¹⁵.

The recent findings suggest that natural products are with less side effects and can be used for the management of different diseases such as diabetes, cancer, hepatotoxicity, and microbial infections^{16,17,18}. Various plant species have been used but, the mode of action of each varies and it has not been subjected to thorough scientific investigations. So scientific exploration to screen drugs for different diseases for the treatment in a natural way will be important¹⁹. Plant based products hold a good therapeutic potential to prevent the abnormalities with additional benefit of low cost. Findings suggest that these plants and their bioactive metabolites are effective in proper functioning like stimulation and suppression based on the abnormalities.^{19,20,21,20,22} Many nanoparticles such as silver, selenium, and zinc oxide play a major role in preventing many diseases including oral mucositis^{23,24,25,26}

PATHOPHYSIOLOGY OF ORAL MUCOSITIS:

A biological model for chemotherapy and radiotherapy induced oral mucositis proposed by various authors appeared to be more generally applicable to alimentary mucositis²⁷. The fundamental mechanism for radiation induced and chemotherapy induced mucositis is believed to be similar²⁸. The pathogenesis of mucositis undergoes five stages which is of

1. Initiation of tissue injury : where chemotherapy/ radiation induced cellular damage resulting in death of basal epithelial cells. The generation of reactive oxygen species by radiation or chemotherapy will lead to initiation of mucosal injury²⁹.
2. Upregulation of inflammation through signal : The free radicals activate second messengers that transmits signals from receptor on the cellular surface to the inside of the cell. Which leads to tissue injury and cell death.³⁰
3. Signalling and amplification : Up regulation of pro inflammatory cytokines such as tumour necrosis factor- alpha, produced by macrophage, causes injury to mucosal cells and also activates molecular pathways that amplify mucosal injury^{31,27}.

4. Healing: This phase is characterised by epithelial proliferation as well as cellular and tissue differentiation, restoring the integrity of epithelium.³². The degree and extent of oral mucositis that develops in any particular patient and site appears to depend on factors such as age, gender, systemic diseases as well as tissue specific factors.³³. In some cases it is indicated that pathways associated with pro-inflammatory molecules including cyclooxygenase-2, nuclear factor kappa and IL-6 are upregulated in oral mucositis.³⁴.

CLINICAL MANAGEMENT OF ORAL MUCOSITIS:

The management of oral mucositis has been largely palliative although targeted therapeutic management has been developed. There are several guidelines for management of oral mucositis.⁸

Pain control :

The primary symptoms of oral mucositis is pain, which significantly affects the food intake, mouth care and quality of life. Using saline mouth rinse, ice chips and mouth rinses containing 2% of anaesthetic lidocaine.³⁵. Some other topical mucosal biocompatible agents are also available but these are not anesthetic but are postulated to reduce pain by forming a protective coating over ulcerated mucosa.³⁶.

Nutritional support :

Uptake of nutrition is compromised by pain associated with severe oral mucositis. In addition taste change can also occur secondary to chemotherapy and or of due to radiation therapy.³⁷. Soft diet and liquid diet is recommended when oral mucositis is present. In case of patients undergoing Hematopoietic cell transplantation total parenteral nutrition is given through indwelling catheter, like Hickman line.³⁷.

Palliation of mouth :

Patients undergoing cancer therapy often develop transient or permanent Xerostomia and hyposalivation³⁸. Chewing of sugarless gum to stimulate salivary flow. Sip water as needed to alleviate mouth dryness, using of cholinergic agents as necessary.⁹

Management of bleeding:

Patients with thrombocytopenia, as a result of high-dose chemotherapy (eg, hematopoietic cell transplant recipients), bleeding may occur from the ulcerations of oral mucositis.^{16,38} Local intraoral bleeding can usually be controlled with topical hemostatic agents such as fibrin glue or gelatin sponge^{39,40}. Patients platelet counts below 20,000/ml may receive platelet transfusion because of the risk for spontaneous internal bleeding, which may have grave consequences especially in the central nervous system.³⁹.

MANAGEMENT OF ORAL MUCOSITIS :

Several agents have been tested to reduce the severity of mucositis or its prevention.

Cryotherapy:

It has been hypothesised that topical administration of ice chips to the oral cavity during administration of chemotherapy results in decreased delivery of chemotherapeutic agents to the oral mucosa¹⁷. It is mediated through local vasoconstriction and reduced blood flow⁴¹. The cryotherapy reduces the severity of oral mucositis. Ice chips are placed in the mouth beginning 5 minutes before administration of chemotherapy and replenished as needed for up to 30 minutes^{42,25}.

Growth factors :

The pathogenesis of oral mucositis mainly involves proliferation of epithelial cells. Thus various growth factors can increase epithelial cell proliferation⁴³. Growth factors like recombinant human Keratinocyte growth factor-1 significantly reduces oral mucositis in patients with haematologic malignancies.^{44,38}. Intravenous human fibroblast growth factor -20 is used currently in reduction of mucositis secondary to high dose of chemotherapy.^{45,46,47}

Low level laser therapy (LLLT):

Low level laser therapy can reduce the severity of chemotherapy and radiation induced oral mucositis²⁶. As LLLT reduces the levels of reactive oxygen species and pro inflammatory cytokines which involves in pathogenesis of mucositis¹⁸. The usage of LLLT requires adequate training and technology.⁸.

Antioxidants :

Amifostine is thought to act as a scavenger for harmful reactive oxygen species that are known to potentiate mucositis^{19,23,24}. Also the use of amifostine was recommended for the prevention of esophagitis in patients receiving chemo radiation.^{20,48} RK 2020(Rx-kinetix) consists of antioxidants N-acetylcysteine in a proprietary matrix for topical application in the oral cavity.^{7,49}

Anti inflammatory agents :

Benzydamine hydrochloride is a non steroidal anti inflammatory drug used to inhibit proinflammatory cytokines including TNF - alpha¹⁸. This can be applicable for patients receiving moderate dose radiation therapy⁵⁰. Glutamine may reduce mucosal injury by reducing the production of proinflammatory cytokines and cytokines related apoptosis^{51,38}

ECONOMIC IMPACTS :

Chemotherapy patients with significant oral mucositis require supportive care measures such as use of total parenteral nutrition, fluid replacement and prophylaxis against infection^{21,52}. Radiation induced oral mucositis also has a significant economic impact because of the cost associated with pain management,⁵¹ liquid diet ,management of secondary infections and hospitalisation.⁵³

CLINICAL CONSIDERATIONS OF ORAL MUCOSITIS :

Chemotherapy induced oral mucositis ,lesions are usually limited to non keratinised surfaces like soft palate , buccal mucosa ,lateral and ventral tongue . The severity of oral mucositis is directly proportional to the dose of the radiation administered . One who receives radiation more than 5000 mc to the oral mucosa will develop severe ulcerative oral mucositis. Rebamipide is a relatively new mucoprotective agent which enhances preservation of existing epithelial cells and replacement of lost tissue through a multitude of actions. Recent studies have shown varied success of Rebamipide in the management of chemoradiotherapy induced mucositis.^{54,55} Topically applied melatonin in the evacuated sockets following tooth removal reduced oxidative stress and inflammation and accelerated the

healing process. Thus, by being directly deposited in the oral cavity, it has the capacity to treat oral disorders and pathologies by reducing inflammatory responses in the gingiva and periodontium.⁵⁶ Phytochemicals, such as Curcumin, turmeric extract, has attracted great attention for its therapeutic benefits in clinical oncology due to its chemopreventive, antitumoral, chemo sensibilizing and radio sensibilizing activities against various types of oral complications.⁵⁷

Conclusion

This is a chronic ulcerative lesion that affects the oral health . Based on the development of clinical and scientific knowledge standard treatment plan and further research and analysis is needed for management of mucositis. The severity of oral mucositis also may be controlled by advanced plant based or nano based phytochemicals.

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