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Approaches to Radiation Mucositis - Understanding Causes, Risks and Treatment Options

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Abstract: ***Radiation therapy is frequently employed in the treatment of head and neck cancers, but it often results in radiation - induced oral mucositis, which is a painful inflammation of the oral mucosal membranes. This condition can significantly affect patients, leading to discomfort, difficulties in eating, and an elevated risk of infections, all of which may prolong the treatment process. The development of mucositis occurs in several stages: initiation, inflammation, ulceration, and healing. Various factors, including smoking, age, and inadequate oral hygiene, can intensify its severity. Effective management strategies aim to provide symptomatic relief, ensure proper oral hygiene, and include interventions such as mouth rinses, analgesics, and emerging therapies like herbal treatments and low - level laser therapy.***

Keywords: oral mucositis, radiation therapy, pain management, ayurvedic medication

1. Introduction

Radiation therapy (RT) is a widely used treatment modality, particularly for cancers of the nasopharynx, larynx, and oropharynx. While RT is effective in targeting and destroying cancer cells, it has an array of complications, especially when confined to the head and neck regions. Patients undergoing RT for head and neck cancers frequently experience side effects, including mucositis, xerostomia (dry mouth), infections (bacterial, fungal, or viral), dental caries, loss of taste, and osteoradionecrosis[1]. Radiation induced oral mucositis is a term emerged in 1980's and defined as an acute toxicity reaction of radiotherapy characterised by normal tissue injury lasting between 7 - 98 days, and begins as an acute inflammation of oral mucosa, tongue, and pharynx during radiotherapy. This can result in a sequela of complications of life - threatening conditions, resulting from - impairment in nutritional intake causing subsequent weight reduction, septic complication from loss of epithelial barriers, interruption or alteration of radiation dose prolonging the treatment time and hospitalization.

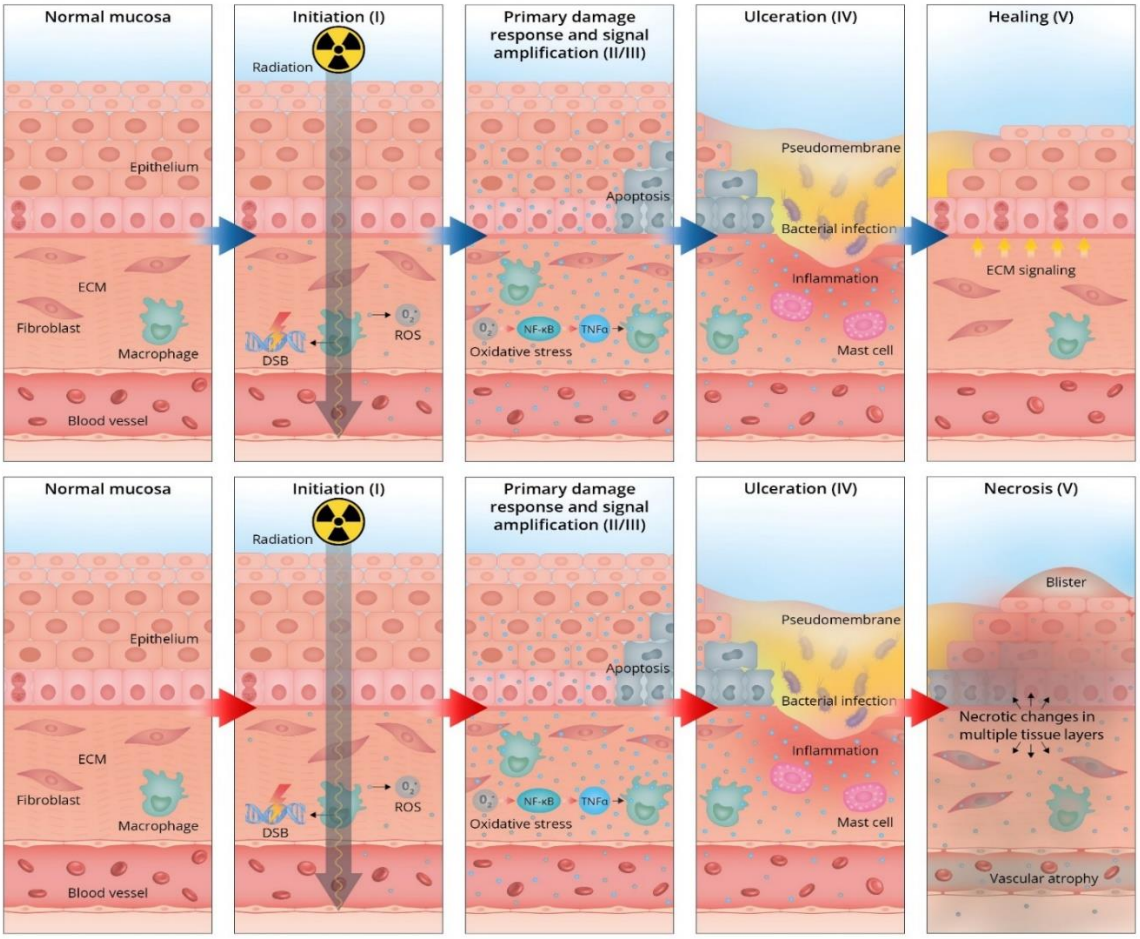
Oral mucositis - risk factors

Among the immediate effects of radiation therapy, Oral mucositis is a significant complication, with an incidence rate of 85% to 100% among patients undergoing head and neck radiotherapy[2]. Mucositis is characterized by painful inflammation of the mucosal membranes, leading to symptoms such as erythema, pseudo membrane formation, and ulceration of the oral mucosa. Chan et al, in a study conducted on Taiwanese population has identified significant predictors for radiation induced oral mucositis as cumulative radiation dose, smoking, and body mass index (BMI). Furthermore, an increase in age, female gender, poor oral hygiene status, smoking, previous cancer treatment, poor renal function, and reduced salivary secretion has been attributed to be the major patient linked risk factors for oral mucositis[2]. The severity of oral mucositis can be so intense that approximately half of the patients who develop severe ulcerative oropharyngeal mucositis, particularly in stage IV may require regimen modifications, and additional hospital stay in between their cancer treatment.

Aetiology and pathophysiology[4]

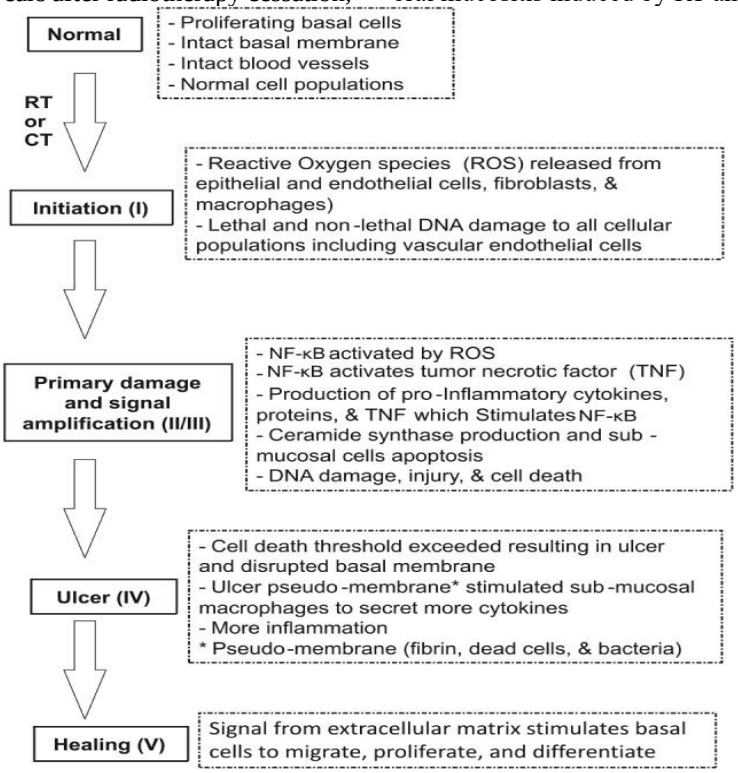
The pathophysiology of mucositis is characterised by five phases - initiation, message generation phase, signalling and amplification phase ulcerative phase and healing phase. The inflammatory phase is characterised by RT - induced tissue injury which results in the release of inflammatory cytokines, e. g., interleukin (IL) - 1β, prostaglandins (PGs), tumour necrosis factor - α (TNF - α), and transcription factors such as nuclear factor kappa B from the resident cells such as epithelial, endovascular, and connective tissue. These mediators might increase the damage by increasing the vascular permeability, leading to more infiltration and recruitment of inflammatory cells and clinically erythema will appear. On the other hand, there are some anti - inflammatory cytokines, such as IL - 10 and IL - 11, that work to minimize the injury. The second phase is characterised by epithelial proliferation and begins within a week of the apoptotic effects of radiotherapy. In addition, bacterial colonization appears and causes the release of new pro - inflammatory cytokines. After a week, the ulcerative phase starts and the ulcer, pseudo membrane and exudation develop[3]. The healing phase starts by matrix signalling to basal epithelial cells to migrate, proliferate, and differentiate. Once the treatment has been stopped, the patient will have symptomatic relief, the healing phase continues, and the mucosa progressively gets back to its normal, but the unresolved neovascularisation persists[2].

Molecular mechanism of radiation induced oral mucositis.



Current five - phase pathobiological model of oral mucositis. (Reprinted from Sonis ST. A Biological Approach to Mucositis. J Support Oncol 2004; 2: 21–36). Macroscopic signs of erythema (Phase II) may be present 2 weeks after initiation of radiotherapy and can progress to pseudo membrane formation (Phase IV) within 3 - 5 weeks after starting radiation. Weeks to years after radiotherapy cessation, mucosal tissues may either heal (Phase V) or progress to necrosis.

Redding's summary of RT and/or chemotherapy (CT) - induced oral mucositis pathobiology. Redding has summarized the pathobiology phases of radiation - induced oral mucositis induced by RT and/or CT.



Clinical features and complications[5]

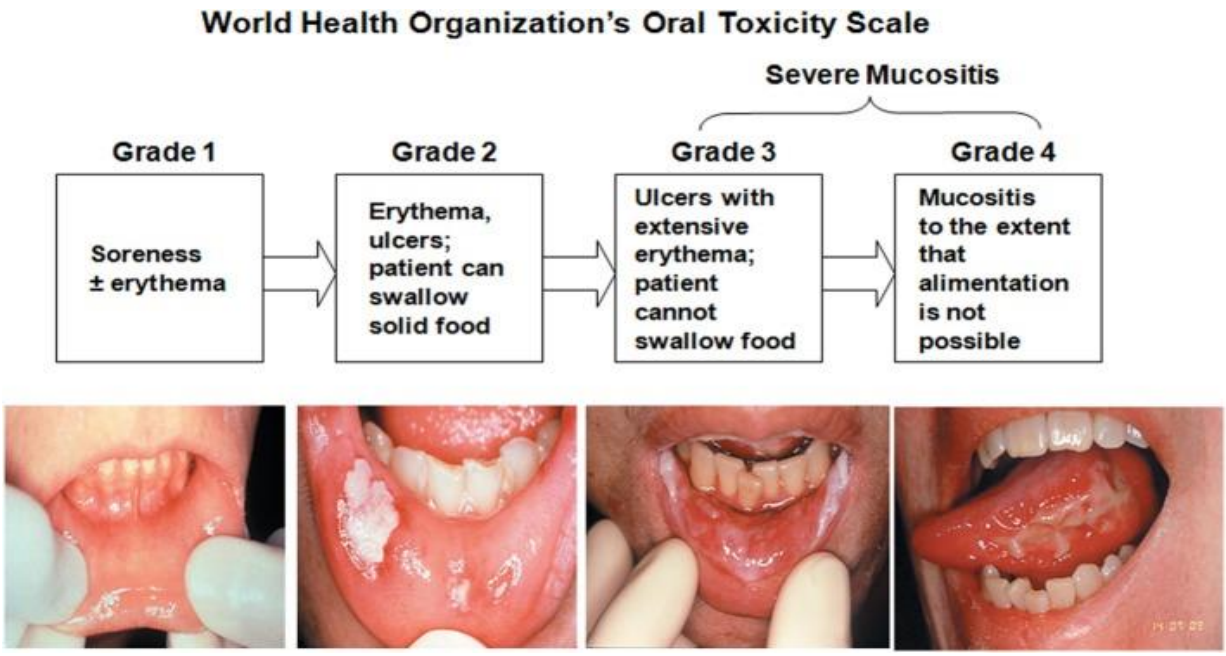
Mucositis develops in rapidly dividing cells in the oral cavity and gastrointestinal tract. Being a localised treatment modality, radiotherapy results in mucositis of the specific irradiated area while chemotherapy affects the entire mucosal area of the body. Concurrent chemotherapy and or fractioned radiotherapy can increase the severity of mucositis. The first sign of the mucositis appears as erythema at the end of the second week (stage I). Followed by it, desquamation appears at 3rd week (stage II). By fourth to fifth week the patient will have confluent mucositis (stage III), ulceration covered with pseudo membrane, and it warrants stoppage of radiotherapy to prevent permanent mucosal injury. Stage IV of the oral mucositis can result in excessive bleeding, necrosis and ulceration. Clinically, the patient will be asymptomatic during the stage I with minimal intolerance to hot/spicy food. Stage II is characterised with pain and burning sensation in oral cavity but with adequate alimentation. From stage III onwards patients show dysphagia on solid food - but liquid alimentation will be possible. Stage IV is characterised with complete absence of alimentation resulting from the severity of oral mucositis. Swallowing and speech abnormalities contributes to further weight loss and morbidity. In immunocompromised patients, it is further worsened by recrudescent herpes and candidiasis. In radiation - induced oral mucositis, non - keratinized tissues affected more often. Most patients who have received more than 50Gy to the oral mucosa will develop severe ulcerative oral mucositis and the severity is directly proportional to the amount of radiation received. Significant clinical outcomes have been observed in patients with high grade oral mucositis. These include feeding tube placement, opiate use for pain control, prolonged hospital stays, increased rate of readmissions, neurocognitive alterations, financial and mental burden, nutritional imbalance, fatigue, anaemia and anorexia as well in an already cachexic patient.

Chemotherapy induced oral mucositis - erythema ans ulceration of the oral mucosa

Radiotherapy induced oral mucositis - diffuse mucosal involvement and radiation caries

Scoring system and diagnostic tests

The incidence of oral mucositis is estimated to occur within or 2 weeks after the beginning of radiation therapy. The severity of the radiation - induced mucositis can be assessed with an oral mucosal assessment guide and assist in early detection of the condition. Other scoring scales introduced by WHO, RTOG and WCCNR have been widely used for assessing the severity and status of radiation - induced oral mucositis. Estimation of CBC and Differential count will help to determine the most susceptible time for the development of oral mucositis and oral infection. The renal and liver diseases are contributing factors for the development of Oral mucositis; hence the serum chemistry level should be regularly monitored to assess the mucosal health status during the treatment period.



World Health Organization's Oral Toxicity Scale. Republished from - Dr. Patrick Stiff, Loyola University Medical Center, Maywood, IL, USA. RTOG, Radiation Therapy Oncology Group; WCCNR, Western Consortium for Cancer Nursing Research; OM, oral mucositis.

Grade	0	1	2	3	4
WHO	None	Soreness ± erythema	Erythema, ulcers, and patient can swallow solid food	Ulcers with extensive erythema and patient cannot swallow solid food	mucositis to the extent that alimentation is not possible
RTOG	None	Erythema of the mucosa	Patchy reaction <1.5 cm, non - contiguous	Confluent reaction >1.5 cm, contiguous	Necrosis or deep ulceration, ±bleeding
WCCNR	Lesions: none	Lesions: 1–4	Lesions: >4	Lesions: coalescing	N/A
	Colour: pink	Colour: slight red	Colour: moderate red	Colour: very red	
	Bleeding: none	Bleeding: N/A	Bleeding: spontaneous	Bleeding: spontaneous	

Toxicity grading of oral mucositis (OM) according to World Health Organization (WHO) and National Cancer Institute Common Toxicity Criteria (NCI - CTC) criteria.

Side effect	Grade - 0 (none)	Grade - 1 (mild)	Grade - 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
NCI - CTC chemotherapy - induced stomatitis/pharyngitis (oral/pharyngeal mucositis)	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, oedema, or ulcers, but can eat or swallow	Painful erythema, oedema, or ulcers requiring intravenous hydration	Severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation
NCI - CTC mucositis due to radiation	None	Erythema of the mucosa	Patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and non - contiguous)	Confluent pseudomembranous reaction (contiguous patches generally >1.5 cm in diameter)	Necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
NCI - CTC stomatitis/pharyngitis (oral/pharyngeal mucositis) for bone marrow transplantation studies	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers, but can swallow	Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia

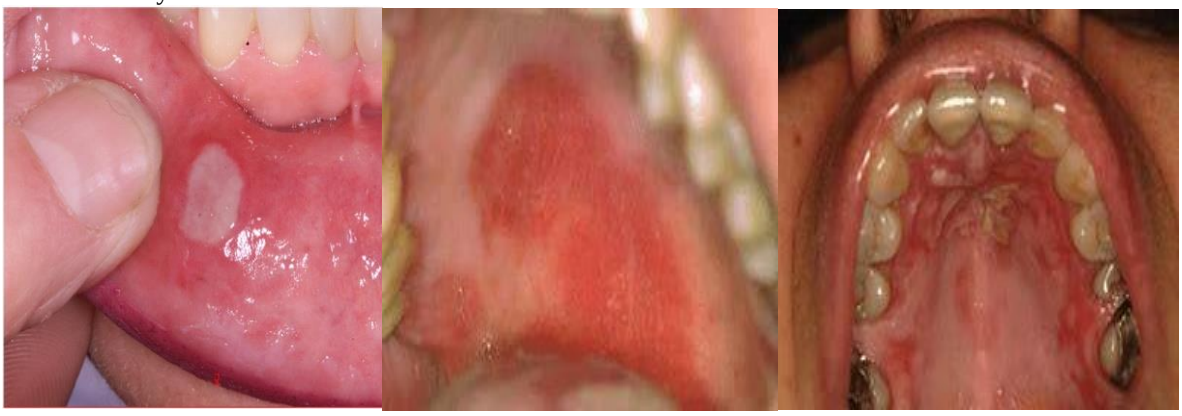
Differential diagnosis of oral mucositis[1]

The conditions commonly mimic oral mucositis includes traumatic ulcer, major aphthae, erosive lichen planus, atrophic candidiasis, herpes simplex infections, vitamin deficiencies and oral malignancies. Proper clinical evaluation and history taking along with laboratory investigations can aid in the definitive diagnosis of the condition.

Disease/injury	Cause	Clinical presentation/lab findings	Severity	Treatment options
Oral mucositis	Chemotherapy and radiation therapy	Diffuse redness, ulcerations, and pain, particularly in areas where teeth abut tissue	Varies; in BMT setting up to 98% have grade 3/4	Palliative rinses, narcotics, palifermin in the BMT setting
Aphthous stomatitis	Etiology not identified - Multifactorial	Single painful ulcer	Localized, but painful; maximum grade 2	Topical
Herpetic mucositis	HSV1	Usually several spots; ulcerative	Usually grade 1–2	Acyclovir, valacyclovir, foscarnet
Oral thrush	Candida	Varies from painless to mild soreness; whitish plaques	Usually grade 0–1	Nystatin rinses; fluconazole and other azoles
Denture/oral trauma	Dentures	Common in elderly patients with loose - fitting dentures	Can limit calories	Repair, removal of dentures
Gangrenous stomatitis	Bacterial infections	Necrotic pseudo membranes	Rare, can be severe	Antibacterials that treat oral aerobes and anaerobes
Acute necrotizing stomatitis	Bacterial infections in immune - deficient patients	Pain, fever, necrotic, bloody ulcers	Grade 3/4	Control of infection

Clinical pictures of the conditions resembling oral mucositis

Aphthous stomatitis erythematous candidiasis Oral burns



Traumatic ulcer ANUG

Management of oral mucositis.

Given the high incidence and severity of mucositis, its management is a crucial aspect of radiation therapy for head and neck cancers. The management modalities are mainly centred on providing symptomatic relief, nutritional support, palliative care/pain reduction, management of secondary infection and oral prophylaxis and categorised under the following as general oral care protocols, interventions to reduce the mucosal toxicity, immunomodulatory agents, topical anaesthetics and analgesics, antiseptics, antibacterial, antifungal and antiviral agents, mucosal barriers and coating agents, cytoprotectants, mucosal cell stimulants, and psychotherapy. Maintaining good oral hygiene is one of the most effective routes to reduce the chances of occurrence and progression of oral mucositis. This will help to minimise the risk of candida growth and secondary bacterial infection.

1) Benzydamine rinses

Among the interventions, mouth rinsing has gained popularity due to its convenience. The most used oral mouth rinse in the clinics is the benzydamine oral rinses - Kazemian et al have identified a 2.6 times reduction in oral mucositis severity on using benzydamine oral rinses compared to the placebo, due to its anti - inflammatory actions. It alters the rate of prostaglandin produced, thus reduces inflammatory response as reported by Epstein *et al*. The use of benzydamine was

reported in six studies yielding a preventive fraction ranging from 19%–44.4% for reduction in pain and 15%–38% for reduction in clinical grades of mucositis. Side effects such as burning sensation, stinging, taste alteration, and excessive numbness were reported in two studies.

2) Anaesthetics and analgesics.

Being the major symptom of oral mucositis, pain relief can be achieved with the help of oral rinses, topical anaesthetics (lidocaine (2%), benzocaine), combination mouthwashes, and the mucosal surface protectants such as hydroxypropyl cellulose gels or sucralfate solutions (in chemotherapy - induced oral mucositis) Chaudhary et al. has proposed it as the starting point of the stepwise approach parallel to the WHO analgesic ladder. For patients with severe mucositis, systemic analgesics including opioids have been suggested in addition to the routine topical medications. Morphine mouth gargles and Doxepin oral rinse have been shown to lower the oral mucositis pain compared to placebo in a randomized, double - blind trial involving 155 patients conducted by Leenstra et al. It activates peripheral opioid receptors and aids in pain relief. Chlorhexidine mouth gargles are recommended for the prevention of chemotherapy - induced oral mucositis, but no proof is available regarding its efficacy on radiotherapy - associated mucositis.

3) Phenytoin combinations

In a study conducted by Baharvand et al, phenytoin - diphenhydramine plus kaolin pectate has shown to be effective in shortening the healing time of mucosal ulcers, improving blood circulation and reduction in pain by 33.1% owing to the properties of its individual components. It was well tolerated by the patient and no side effects were reported.

4) Salts

Salts of sodium, calcium and bicarbonate rinses have proven to moisten, lubricate, neutralises and clean oral cavity. There were no significant effects found on the reduction of frequency, duration, and severity of oral mucositis in the studies by Stokeman et al. However, it yielded a preventive fraction of 1.9%–33.3% for reduction in clinical grades of mucositis and 7.6%–11.3% for reduction in pain with no reported side effects.

Recent advancements in the treatment of oral mucositis

1) Topical medications and interventions.

a) Topical agents - Other topical modalities undergone clinical and randomised trials include - GM CSF - granulocyte - monocyte colony stimulating factor (due to its wound healing and keratinocyte proliferation activities in human skin), polymyxin E, tobramycin, and amphotericin B - lozenges (owing to oral decontamination effects), Palifermin (reduces the severity, duration and prolongs the time for the development of oral mucositis.), and Glutamine (delays and reduces Grade III mucositis.).

b) Interventions -

- The other agents include Low Level Laser Therapy (LLLT), and beta carotene - owing to their antioxidant action on free radicals released during radiotherapy. The use of LLLT induces an anti - inflammatory, analgesic, and wound - healing effect in the tissue via the modulation of reactive oxygen species and activation of transcription factors, leading to increased cell proliferation and migration in radio, chemo and combination therapy and the results are in concordance with the guidelines of Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines for Mucositis 2021.
- Cryotherapy can be used for the prevention of chemotherapy induced oral mucositis considering its mechanism of action of vasoconstriction resulting in reduced oral drug concentration and toxicity during chemotherapeutic cycles. However, evidence regarding its effect on radiotherapy hasn't been documented. Palifermin (keratinocyte growth factor - KGF) was shown to be effective in patients with solid tumours receiving radiotherapy. Later it was found out that, its efficacy depends upon the type of cancer treatment. Currently, this FDA approved drug is only used in patients with high doze chemo and radiotherapy undergoing stem cell rescue.
- Low temperature atomization inhalation (LTAI) on in vitro study has showed increased cell viability and reduced cytokine production (IL - 6 and TNF - α) which in turn can be used for a preventive modality for oral mucositis based on its inhibitory action on inflammatory response, mucosal oedema and pain sensitivity.
- Zinc chloride has the properties of stabilising cell membranes and increasing protein synthesis and can be used in mouth rinse form for the reduction in the incidence of chemotherapy induced oral mucositis.
- Intravenous Actovegin along with a proper oral regimen has shown a progress in reducing chemotherapy induced oral mucositis.

2) Herbal remedies for oral mucositis.

Apart from the allopathic medications, several natural, herbal and ayurvedic products have been proven to be effective in the management of chemoradio - induced oral mucositis. Natural honey, calendula flower extract, curcumin, Kangfuxin and clove-based mouth rinses were reported in single studies each, with the highest preventive fraction for honey-based mouth rinse (77.8%) and the least for clove-based mouth rinse (16%). The mechanism of action of these formulations was not clearly mentioned, and none of the studies reported adverse effects. Honey and propolis (bee glue) have been widely used as prophylactic measures for chemo - radiation induced oral mucositis. Honey reduces wound pain by delaying tissue oxygenation by blocking exposure of the damaged mucosa to oxygen. Biswal et al suggested that the effectiveness of honey on wound healing might be because of its viscosity, hygroscopic nature, and the acidic pH. Sonis et al. described that the analgesic and anti-inflammatory activity of honey is due to inhibition of the signal amplification by pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-1 (IL-1), and IL-6. The propolis has a high concentration of flavonoids and phenolic compounds which delays the appearance of the mucosal lesions. Aloe vera has also been shown to have anti - ulcerogenic and anti - inflammatory activity in reducing radiation - induced oral mucositis. Other herbal agents including medicinal plants, have shown to reduce the severity of oral mucositis - rooting

from its chemical composition comprising polyphenols, carotenoids, triterpenes and essential oils.

The summary of treatments with natural products for mucositis in cancer patients, converted into a table format - done by Agarmohammadi et al[8].

Product	No. Patients	Type of Use	Treatment	Results
Honey	40	Topical and swallow	Combined chemo and radiotherapies	Significant reduction in grade 4 mucositis, Candida colonization, and positive cultures for aerobic pathogenic bacteria in the honey group
Propolis (bee glue)	40	Topical and swallow	Chemotherapy	Not statistically significant
Coffee plus honey	75	Topical and swallow	Chemotherapy	The best reduction in severity was achieved in the coffee plus honey group. Honey group and steroid group ranked second and third
Matricaria recutita	164	Topical (mouthwash)	Chemotherapy	No difference in frequency of mucositis
Peppermint	40	Topical (mouthwash)	Chemotherapy	Significant reduction in frequency of mucositis
Aloe vera	61	Oral juice	Radiotherapy	Significant reduction in frequency of mucositis
Calendula officinalis	40	Topical (mouthwash)	Chemo - radiotherapy	Significantly decreased the intensity of mucositis
Olive leaf extract	30	Topical (mouthwash)	Chemotherapy	Significantly decreased the intensity of mucositis
Glycyrrhiza glabra	45	Topical (mouthwash)	Radiotherapy	Result showed better outcome for mucositis
Curcuma longa	7	Topical (mouthwash)	Chemotherapy	Reduction in the WHO, OMAS, and VAS scores of oral mucositis
Extract of human placenta	60	Intramuscular	Radiotherapy	Decrease in pain and progression to grade 3 mucositis and improvement in difficulty with swallowing was observed

1) Ayurvedic management[13, 14]

Various ayurvedic medications have been indicated for the prophylactic and preventive therapy of oral mucositis. The most used modalities include mouth kaavalas, churnas and gandushas. Yashtimadhu/ Glycyrrhiza glabra is a commonly used Ayurvedic and Chinese medication, with proven pharmacological actions such as antiulcerogenic, anti - inflammatory antioxidant and antimicrobial properties. The study conducted by Mamgain et al noted a significant alleviation of mucositis - induced symptoms in patients treated with yashtimadhu. Triphala Rasayana was more effective than the nonsteroidal anti - inflammatory drug, indomethacin, in ameliorating pain and inflammatory effects. Triphala reduced the expression of inflammatory mediators such as IL - 17, COX - 2, and RANKL through inhibition of NF - kB activation - one of the main mechanisms in radiation - induced mucosal inflammation. Haridradi Taila revealed highly significant in relieving symptoms like ulceration present in the buccal mucosal layer, burning sensation of palate, redness and erosion of the oral cavity, difficulty in swallowing & chewing pungent things, enlargement of lymph nodes.

Available studies of effectiveness of ayurvedic medication on chemo/radiation induced oral mucositis[13].

Author (s)	Study Subject	Treatment	Findings
Woon Sup Yoon et al.	Sprague Dawley rats	Thriphala for radiation - induced acute intestinal mucosa damage	Showed positive effect of Thriphala in reducing radiation - induced acute intestinal mucosa damage
RK Mamgain et al.	Head - and - neck cancer patients	Ayurvedic preparation of Yashtimadhu (Glycyrrhiza glabra) along with conventional management	Yashtimadhu was effective, delaying the development of severe mucositis compared to conventional management alone
Ahmadi A	Patients undergoing radiotherapy	Oral aloe vera mouthwash	Aloe vera has anti - inflammatory and wound healing properties, potentially preventing radiation - induced mucositis
Su et al.	Patients undergoing radiotherapy for head and neck cancer	Oral aloe vera mouthwash	Concluded that aloe vera was not a beneficial adjunct to radiotherapy, as it did not decrease mucositis or improve patient well - being
Naidu MU et al.	Patients with oral mucositis	Mixture of herbal agents in an oral gel wafer (glycyrrhizin, Centella asiatica, Polygonum cuspidatum, Angelica sp, and Camellia sinensis)	Positive effect observed in a pilot study for managing oral mucositis, but further studies are needed to confirm the results
Randomized clinical trial by Aghamohamamdi A et al	Head - and - neck cancer patients requiring radiation	Pure natural honey (from thyme and astragale) applied before and after radiotherapy	Significant reduction in mucositis was observed in patients treated with honey compared to controls
Randomized clinical trial Biswal BM et al	Patients undergoing radiotherapy	Pure honey (20 mL before and after radiation therapy)	Similar results showed reduction in mucositis with honey application
Clinical trial comparing 0.15% Benzydamine HCl and natural honey.	Patients undergoing radiotherapy	The patients were randomized into three groups of 20 patients. Group 1 patients received topical application of natural honey; groups 2 and 3 received topical application of 0.15%	The onset of mucositis and the severity of mucositis were graded during the radiotherapy and 2 weeks after radiotherapy. A significant reduction of mucositis in patients treated with honey was compared with 0.15% benzydamine

		benzydamine hydrochloride and 0.9% normal saline, respectively.	hydrochloride, 0.9% normal saline applied to patients was observed.
Shinobu Okadaet. al	a pilot study in hematopoietic cancer patients	with topical application of sesame oil	Retardation of chemo - radiotherapy induced oral mucositis. Cytological evidence of reduction in chemotherapy induced inflammation.

2) Others -

a) N - Acetylcysteine (NAC): This compound contains thiol groups and plays a role in antioxidant processes by reducing reactive oxygen species (ROS) production, myeloperoxidase activity, and xanthine dehydrogenase and xanthine oxidase activity[15]. Additionally, it contributes to the inflammatory response by activating NF - kB. In a double - blind, randomized study, Moslehi et al. found that leukemic patients receiving NAC had a significantly lower rate of oral mucositis (OM) compared to those receiving a placebo. NAC, besides its antioxidant properties, also modulates various pathways relevant to mucositis pathogenesis, including NF - κB.

b) Superoxide Dismutase Mimetics: These mimetics target superoxide dismutase and are currently being evaluated in a phase 2 trial (NCT02508389) (ClinicalTrials. gov, 2017a) [16].

2. Conclusion

Oral mucositis has found to be one of the common oral conditions to the patients in the initial weeks of chemo and or radiotherapy. The self - limiting and debilitating condition negatively affects the patient's quality of life, prolongs the treatment period and cause interruptions in the cancer therapy. The etiopathogenesis is mainly centred around the free radical production and cascades of inflammatory reactions occurring locally in the mucosal surface from the chemo/radio therapy interventions. The clinical features along with scoring criteria can be used for assessing the status and severity of the oral mucositis. The prognosis of the condition is found to be good unless and until the patient is severely debilitated or severe systemic difficulties appear. Various medical interventions have been proposed including topical & systemic agents, preventive medications, ayurvedic interventions, laser/cryotherapy and herbal agents. Maintenance of oral hygiene and preventive therapies along with constant follow up will help to lower the severity of this condition, and it will resolve in most of the patients by the end of the therapy.

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