Review Article

Oral mucositis

ABSTRACT

Oral mucositis is one of the most common complications of cancer therapy. It is a nonhematologic complication of cytotoxic chemotherapy and radiotherapy and reduces the quality of life. It is estimated that 40% the cases on standard chemotherapy may develop oral mucositis. Patients receiving radiation, especially in the cases of head and neck cancer, have 30%–60% chances of developing mucositis. Chemotherapy and radiotherapy interfere with the normal turnover of epithelial cells, leading to mucosal injuries. These injuries can also occur due to indirect invasion of Gram negative bacteria and fungi as most of the chemo-therapeutic agents will cause neutropenia and will give a favorable environment for the development of mucositis. The patient-related factors are also responsible for developing mucositis in chemo-induced and radiation-induced mucositis. Poor oral hygiene may also be responsible for bacterial super infection followed by chemotherapy. Mucositis is of two kinds: direct and indirect mucositis. Direct mucositis - The epithelial cells of the oral mucosa undergo rapid turnover in usually 7–14 days due to which these cells are more susceptible to the effect of the cytotoxic therapy which results in oral mucositis. Indirect mucositis – it can develop due to the infection caused by Gram-negative bacteria and fungal infection. There will be a greater risk for oral infection due to neutropenia. The onset of mucositis secondary to mylo-suppression varies depending upon the timing of the neutrophil count associated with chemotherapy agents but they typically develop around 10–21 days after chemotherapy administration.

Keywords: Chemotherapy, mucositis, radiotherapy, traditional medicine

INTRODUCTION

It is an inflammatory mucosal lesion which has developed as a result of chemotherapy or radiation therapy. It can sometimes impair the quality of life and may lead to the discontinuation of the therapy due to reduced immunity. The mucosal lesions can be unreliable, painful and expensive for the patient and the caregiver. It occurs in up to 40% of the cancer patients who received chemotherapy and 80% of the cases of head and neck cancer who received radiotherapy.[1]

The oral complications can be divided in two groups: acute and late complications. An acute complication occurs during therapy and a late complication occurs after therapy. Acute complications may include oropharyngeal mucositis, xerostomia, sialadenitis, fungal and viral infections, and taste dysfunction. Late complications are mucosal fibrosis and atrophy xerostomia, tissue necrosis, taste dysfunction, and dysphagia. The etiopathogenesis of mucositis caused by radiation is different than that caused by chemotherapy.

Access this article online	
Website: www.njms.in	Quick Response Code
DOI: 10.4103/njms.NJMS_10_20	

As the severity of mucositis increases, the topical pain management strategies become less effective and it may become necessary to depend on systemic analgesics.[2-4]

Head and neck radiation patients have less risk of bleeding. Thus, non-steroidal anti-inflammatory agents should be given for pain control. However, if it is not effective then opioids can be given. Hyposalivation is one of the important findings in patients with radiation and chemotherapy. It can lead to fungal infection. Patients with radiation therapy usually have

Vibha Singh, Akhilesh Kumar Singh[1]

Department of Oral and Maxillofacial Surgery, K.G. Medical University, Lucknow, [1]Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Address for correspondence: Dr. Vibha Singh, Department of Oral and Maxillofacial Surgery, K.G.Medical University, Lucknow, Uttar Pradesh, India.
E-mail: vibhasinghraghuvanshi@gmail.com

Received: 31 January 2020, **Revised:** 21 June 2020, **Accepted:** 13 July 2020, **Published:** 16 December 2020

How to cite this article: Singh V, Singh AK. Oral mucositis. Natl J Maxillofac Surg 2020;11:159-68.

no neutropenia and thus, topical anti-fungal rinse or topical applications can be used. They should be asked to avoid eating, drinking and rinsing for at least 30 min. In case of denture wearers, the denture should also be treated with antifungal agents. In cases of persistent lesions, systemic antifungal should be given.

Direct exposure to oral and pharyngeal mucosa results in damage of taste receptors. Thus, patients cannot discriminate taste and it takes around 6–8 weeks for complete recovery.

- Grade 1-Mild oral soreness, erythema
- Grade 2-moderate – Erythema, ulcers but oral intake is not prevented
- Grade 3-Severe oral ulcers interfering with oral intake and requiring liquid only
- Grade 4-Life-threatening oral ulcers to extent that oral alimentation is impossible.

It begins after cumulative exposure to 15 Gy and worsens markedly if total dose exceeds 60 Gy.

Symptoms control and palliative care in hematopoietic stem cell transplantation.

The WHO Grading system for Oral mucositis.[5]

- Grade 0-No mucositis present
- Grade 1-Irritation of Oral mucosa. with pain no overt ulceration patient have normal diet
- Grade 2-Sore evident in oral mucosa, patient still able to swallow solid food
- Grade 3-Patient experience sensitivity when swallowing solid food, liquid diet is necessary
- Grade 4-Patient unable to swallow total parenteral nutrition or tube feeding is necessary.

FIVE STAGE MODELFOR DEVELOPMENT OF MUCOSITIS

- Stage 1–(Initiation) – This stage, corresponding to the lesion directly, is caused by irradiation or chemotherapy and adversely affects the cells and the strands of DNA in the basal epithelium and the sub mucosa. Free radicals are reactive oxygen species (ROS) also generated and play an interfering role in the biological event of the later stage
- Stage 2-(Upregulating) – The negative effect on, cells, DNA, and ROS activates a cascade of reactions which bring about the production of pro-inflammatory cytokines. These compounds stimulate pathways leading to lesions or the death of basal cells by apoptosis
- Stage 3. (Signal amplification) – The release of pro-inflammatory cytokines not only damage the cells but also provides a positive feedback which amplifies the lesions caused directly by radiation or chemotherapy
- Stage 4. (Ulceration) – This stage is characterized by painful lesions subject to colonization by bacterial proliferation, causes new tissue damage and activates the production and release of additional pro-inflammatory cytokines by infiltrating mononuclear cells
- Stage 5. (Healing) – This phase is characterized by epithelial proliferation as well as cellular and tissue differentiation. Thus restoring the integrity of the epithelium.

Objective scoring system for site assessment

This system of scoring is commonly used for assessing site involvement in cases of oral mucositis induced by chemotherapy which may or may not be associated with radiotherapy.

It is scored from 0 to 3, based on the size of the ulcer.

- Zero-no lesion
- One– size is <1 cm^2
- Two-if size is between 1 and 2 cm^2
- Three-size is >3 cm^2.

It is scored from 0 to 2, based on the severity of erythema.

- Zero-No erythema
- One-non severe erythema
- Two-indicates severe erythema.[1]

PATHOGENESIS

The pathogenesis of mucositis is related to direct mucotoxicity from ionizing radiation. Several anti-cancer agents such as methotrexate and etoposide are secreted in saliva which leads to an increased risk of direct mucositis.

The pathobiology of mucositis has been described in five stages [Table 1]. While no complex physiologic process can be compartmentalized, this step-wise approach provides a conduit to understanding the event that underlie the sequence of oral mucositis.

Two events characterize the initiation phase. Radiation and chemotherapy directly injure DNA and cause strand breaks resulting in clogenic death of basal epithelial cells. Generation of ROS is also a significant event from the standpoint of ultimate tissue damage.

During the primary damage response, chemotherapy, radiotherapy, and ROS initiate a series of interacting biological events transduction pathways triggered by DNA

Table 1: Scale of mucositis

Grade	WHO scale	NCI-CTCAE scale
1	Oral soreness, erythema	Painless ulcers, erythema, or mild pain in the absence of lesion intervention not required
2	Erythema, ulcers, patient can swallow solid food	Painful erythema, edema, or ulcers but eating or swallowing possible modified diet indicated
3	Ulcers with extensive erythema patient cannot swallow food	Painful erythema, edema or ulcers interfering with oral intake, requiring IV hydration
4	Mucositis to the extent that alimentation not possible	Severe ulceration or requiring parenteral or enteral nutrition support or prophylactic intubation
5	NA	Death related to toxicity

NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; WHO: World Health Organization; NA: Not applicable. The WHO Grading system for Oral mucositis.[5] Grade 0: No mucositis present, Grade 1: Irritation of Oral mucosa .with pain no overt ulceration patient have normal diet, Grade 2: Sore evident in oral mucosa, patient still able to swallow solid food, Grade 3: Patient experience sensitivity when swallowing solid food , liquid diet is necessary, Grade 4: Patient unable to swallow total parenteral nutrition or tube feeding is necessary

strands breaks and lipid per oxidation prompt the activation of a number of transcription factors such as NF-Kbwnt P53 and their associated canonical pathways. Chemotherapy and radiation can directly activate NF-kBeta indirectly can be activated by ROS.

There are 200 genes whose expression is governed by NF-β are associated with production of molecules which have activity in the pathogenesis of mucositis including cytokines and cytokines modulators. Stress responders and cell adhesion molecules apoptosis is consequence of the effect of NF-Kβ in normal cells. The indirect cell death pathways such as ceramide pathways are also affected by radiation and chemotherapy as cytotoxic therapy percolates in to connective tissue fibrinolysis. This stimulates macrophases to produce damaging matrix metalloproteinase. This process begins within seconds after radiation and chemotherapy. The destruction of epithelial stem cells starts immediately.

There is a lag between the damage that occurs at the molecular and cellular level and their manifestations as clinical mucositis. In the cases of fractionated radiation, extensive mucositis occurs in daily increments.

Signal amplification many of the molecules induced by primary response have the ability to positively or negatively feedback and alter the local tissue response such as tumor necrosis factor alpha (TNFα) may positively feedback on NF-Kβ to amplify its response and initiate mitogen activated protein kinase signaling. None of these mechanisms occurs in isolation. They may occur simultaneously and through a series of network in which some genes are more controlling and critical than others. The above mechanism inhibits resolution and leads to ulceration. It develops due to direct and indirect mechanism by damage and apoptotic changes to epithelium of oral mucosa these ulcers get colonized by oral bacteria.

The bacterial colonies on ulcer surface are active contributors to the mucositis process. In granulocytopenic patients, there is risk that intact bacteria may invade submucosal vessels to produce bacteremia sepsis. The majority of the cases of oral mucositis heal in due course of time. The patient being treated with chemotherapy mucositis generally has acute event symptoms first begins about 3–5 days after drug infusion ulceration is noted in couple days later and resolve within 2 weeks.

Radiation-induced mucositis has a chronic course over a 7 weeks' period. The ulcerations arise due to radiation ranging from 2 Gy per day to 70 Gy per day. It can also last for 3–4 weeks after the completion of the treatment.

Taste dysfunction - As oral and pharyngeal mucosa is exposed to radiation, taste discrimination becomes increasingly compromised. After several weeks of radiation therapy, patients commonly complain of not having taste sensation. It usually takes around 6–8 weeks after the end of radiation therapy to recover.[1]

Risk factors

The patient at high risk is head and neck cancer population and individuals being treated with high-dose myeloablative chemotherapy. In patients with solid tumor, breast, colon, rectum and lung each cycle of therapy have mucositis risk. If the patient develops mucositis after first cycle the risk will increase in subsequent size, may be in first cycle 20% jumps to 60% in the next cycle. Risk of mucositis may be increased in two ways

1. The association of therapy dose and the route of administration
2. Age, body mass, and gender as potential risk factors. In patients with tongue cancer receiving chemotherapy and radiation therapy, the chances of mucositis is 100%. In patients of hypopharyngeal cancer, the risk drops by up to 50% because tissue is not in direct field of radiation. Genetic factors may also pay a dominant role in determining mucositis risk. Scnwab *et al*. assessed

the productive value of three polymorphism associated with the metabolism of flurouralcle for toxicity risk. They found a significant association between dihydro primidine dehydroginase varients and the development of oral mucositis.

TNF-α appears to play a role in oral mucositis development and many polymorphism control individuals TNF production. Bogunikubik *et al*. evaluated the role of the expression of TNF-α1 and 2 on toxicity risk including mucositis among the patient undergoing allogenic HSCT and found that that was more than twice that attributable to the use of aggressive conditioning regimens. The mechanistic gene-based risk provided by studies who revealed that radiation induced dermatitis has similar pathogenesis of mucositis. ROS plays a very important role in the initiation phase. The cell behavior is influenced by tumor parenchyma and stoma there are the source of molecules which influences the cell behavior. The tumor derived peptides and protein could directly modify normal cell response for radiation and chemotherapy, the metalloproteinases enhances the breakdown of local tissue environment.[1]

THE ORAL ENVIRONMENT AND MUCOSITIS

The oral cavity is the most complex environment in the body. The course of mucositis might be influenced by the local environment neither changes in saliva or microflora are significance in primary etiology of oral mucositis. Uzel *et al*. studied the quantitative and qualitative changes of the oral bacterial flora in an established hamster model of radiation induced mucositis.

The peak bacterial loads co-induced with the peak mucositis scores but an increase in bacterial number lagged behind the development of ulcerative mucositis. Bacterial numbers decrease as findings contradict a hypothesis that suggests that an increase in the bacterial numbers. The observation of a 300% increase in the mean biological load compared to base line suggests that ulcerated mucosa represents a desirable colonization site.

Bacterial numbers decreased as ulcer spontaneously resolved. d, indicating that the presence of large number of organisms was not enough to inhibit healing. There are some studies that reported increase in Gram-negative organisms during ulceration and re-establishment of normal bacterial proportion was required for spontaneous ulcer resolution, irrespective of bacterial numbers. There are clinical trials which suggested that antibacterial strategies have been in effective as oral mucositis interventions. Stimulations in salivary flow as oral mucositis treatment are not successful.[1]

According to the five-plane model for mucositis development, it has been suggested that the transcription on factor NFk-Bact as gatekeeper for various pathways. In recent years, it has been shown that pro-inflammatory cytokines play a key role in both oral and GI toxicities.

Gene expression and tissue levels of TMF-α and IL-1 β were closely correlated with oral and gut mucosa injury following radiation.

The pro-inflammatory cytokines TNF, IL-1 β and IL-6 were also associated with the development of chemotherapy induced GI mucositis.

The elevated level of pro-inflammatory cytokines such as TNF IL-1 β and IL-6 have been identified to be excellent markers of inflammation induced by chemotherapy, Thus, anti-inflammatory agents inhibiting pro-inflammatory cytokines will show reduction in mucositis.[2,17]

MICROBIOME CHANGE[2]

Shift in GI and oral flora reported in mylosuppressed patient, oral flora change in the bacterial flora associated with neutropenia and mucosal surface change are well documented. In the cases of hematopoietic cell transplantation, it leads to neutropenia, xerostomia, followed by bacterial substitution is associated with oral mucositis.

Gut micro biome and its influence on GI mucositis is being increasingly recognized in the field of research. It was believed that the gut microbiota plays a little role in pathobiology of mucositis with bacterial translocation being a secondary outcome of mucosal layer. Degradation is followed by inflammation and apoptosis.

In recent studies, there is a change in commensally bacteria, particularly biofido bacterium species towards salmonella species and *Escherichia coli* following chemotherapy treatment. Stringer *et al*. (2009) demonstrated that increase in commensally bacteria represented by bifido bacterium species inversely flowed the pattern of diarrhea induced by chemotherapy.

It is not yet clear how commensally bacteria influence the different stages of mucositis development. These are responsible for inflammatory process, intestinal permeability, composition of mucosal layer epithelial repair and regulation of immune effect on molecules including toll-like receptors.

Chemotherapy cycle with mucositis is associated with high risk of infection and use of antibiotics.

When it changes in to ulcerative phase there will be translocation of residential microorganism and their bi-products from alimentary canal tract in to blood, most commonly from oral cavity, esophagus, ceacum, and rectum.

The type and dose of cancer therapy also affect severity of mucositis. Clinical observation can be categories into treatment and patient related.[19]

Chemotherapeutics agents known for mucosal injury.

Alkylating agents – Busulfan agents, cyclophosphamide, thiotepa, procarbaziene.

Anthracyclines – Doxorubicin, epirubicin, daunorubicin.

Antitumor agents Actinomycin D, Bleomycin, mitomycin.

Taxanes–Paclitaxel.

Vinca alkaloid–Vincristine, vinblastine.[1]

Biomarkers of mucosal injuries

An emerging class of biomarkers for mucositis is the pro-inflammatory cytokines and matrix metalloproteinase (mmps).They have augmented expression profiles in the alimentary tract in animal model of mucositis.[2]

There is a difference between chemotherapy and radiotherapy-induced mucositis. The biological pathways are slightly different in both cases. Chemotherapy is administered systemically whereas radiation therapy affects a specific body area.

If chemotherapy is delivered in a short time then injury to mucosal tissue will be acute and it will develop between 4 and 7 days after initiation of treatment and will peak within 2 weeks.

Radiotherapy has more gradual clinical course since it is most often administered in small fractions given over weeks. Radiation induced typically begins a cumulative dose about 15 Gy after 10 days and typically reaches full severity at 30 Gy last for weeks even months.[3]

Ulcers other than oral mucositis or non mucositis etiology

Ulceration induced by herpes simplex virus reactivation differs clinically from mucositis in that they may also involve the dorsum of tongue, gingival, and hard palate. The host disease may be present as lichenoid lesion acute graft versus host disease.

Typically GVHD (acute graft vs. host diseases) where desquamation and ulceration develops after engraftment when oral mucositis resolves. This is difficult to distinguish from oral mucositis. Mylosuppressed hematological patients may also develop neutropenic ulcers that are usually well defined and painful. Typically, microbiological tests are negative.[3]

Management

The treatment of mucositis includes patient education, use of non-medicated saline rinse, and topical and systemic agents for pain and infection control.

This can be divided into two parts: supportive treatment for non-pharmacological and pharmacological options.

NON-DRUG TREATMENT

Prevention is better than cure. Strategies involved include pre-treatment dental and oral check-up. To keep oral cavity clean, mouth should be rinsed at least 4 times/day. The use of non-detergent tooth paste and alcohol-free mouth wash is recommended.

Artificialsaliva, dry mouth gums, honey can also be used to keep mouth lubricated to avoid any trauma. Drinking of lots of water at least 3 L/day, and to avoid alcohol intake and smoking. Nutritional care should be taken care of citrus fruit, acidic juice, spicy food hot juice can aggregate mucositis. Soft liquid and nonspicy food should be given to avoid injury to mucosa. Suckling ice cubes will also give soothing effect.[5,18]

Attempt to prevent and treatment of oral mucositis is need of the time apart from excellent oral care exposure to soft LASER administration of keratinocytes growth factors, they have their own limitations. There are many guide lines for management of cancer therapy induced oral mucositis that has been defined by organization including multinational association of supportive care in cancer/International society of oral oncology, the American Society of Clinical Oncology. These guidelines recommended to use oral care program such as dental flossing, non-medicated mouth washes such as normal saline wash.

Natural remedies including herbal extract and dietary supplements plays a very important role in management of mucositis. Nutritional supplements are perceived as needed elements in patients with unbalanced diet.[10] In few cases that Zinc sulfate reduced the incidence and severity of oral mucositis in leukemia patient undergoing chemotherapy.[4]

The use of medicinal plants for ulcers, inflammation and healing of different types of wound is known since ancient time.[6-8,11,18]

Phytochemicals have been identified which are capable of showing beneficial effect for the treatment of tissue injury so they can also be used oral lesions too.[5,10]

Oral preventive cares natural products including herbal extract and dietary products some Chinese herbs and Ayurvedic preparations are also used in management and prevention of oral mucositis. Phytochemical has been identified which are capable of showing beneficial effects for the treatment of tissue injuries so that they can be used for mucositis.[6]

Aloevera gel used thrice per day showed reduced in incidence of oral mucositis.

The herbal agents provide antioxidants propertiesthrough COX-2 suppression and immune modulator mechanism. Although there was no improvement in patients undergoing radiation therapy but the quality of life was improved. There are several studies they showed the same results.

Camellia

The leaf extract of Camellia sinensis leaf extract which participates in the green tea production and palmitoyl hydrolyzed, wheat protein, it seems to neutralize excessive production of ROS and ulcerative destruction in oral mucositis.

Catechu

It has properties of tissue regeneration as well as wound healing properties so it can be used as a mouth wash.

Shi Y and Shan J showed more effects of catechu powder compared to local norfloxacin on oral mucositis. It was used locally in patients who were having chemotherapy. Hence, this can be used as promising treatment for mucositis.

Chamomile

This herb contains several substances such as chamazulene, alpha bisabolol, bisbolol oxides spirometer, and flavonoids with anti-inflammatory, antibacterial, and antifungal effects. In a pilot study, it was evident that it can reduce oral mucositis in cancer patients.

INDIGO ROOT

It is common herb which provides antiviral, fever detoxification, and anti-inflammatory properties. Its anti-inflammatory effect was reported in a clinical trial for patients undergoing for radiation therapy. Patients were asked to gargle with 30 ml indigowood solution for 3 min and then swallowed it before meals. This reduced the severity of radiation mucositis and resulted in a reduction in anorexia and swallowing difficulties too.[6,7,10,11,18] It can also reduce weight loss and serum level of pro-inflammatory cytokines interlukin-6. Another pro-inflammatory cytokines IL-1 beta level was also in the group.

PEPPERMINT[6]

The essence of the peppermint plants offers strong antibacterial and antifungal effects. It can provide a cooling sensation on the mucosa and the skin. Ashktorab *et al*. evaluated the preventive effects of the oral rinse of peppermint on oral mucositis in patient undergoing chemotherapy. They reported efficacy, well tolerance of peppermint oral rinse in the cases of mucositis.

Calendula officinalis L (Marigold)

It is a widely cultivated ornamental plant from the family *Asteraceae*. Several medicinal properties of the plant have been reported, including anti-inflammation and wound healing. This also is considered as a safe topical treatment in radiation-induced dermatitis. In a clinical trial, flower gel was administered from 1st day of radiotherapy by the end of 2nd week intensity of oral mucositis was significantly lower in intervention group as compared to placebo. They do not need any treatment for mucositis. In the same group, 3 patients did not develop mucositis.

Phoenix dactylifera L (Date palm)

It is a tree from *Arecaceae* family which is native of tropical and subtropical climates.

In a pilot study by Elkerm 2014 patients with head and neck cancer were treated with pollens of date palm in the form of suspension and was given once per night it was compared to standard treatment including analgesic and antifungal agents. Reduction in the severity of oral mucositis and reduction in dysphasia was observed.

Leptospermum scoparium

Leptospermum scoparium and *Kunzea ericoides* - It is commonly called manuka and kanuka the mixture of kanuka and manuka in 1:1 ratio essential oil in water the preparation was first gargled then swallowed by patients to reach to areas of the oral cavity more prone for mucositis. There was significant delay in developing mucositis and less consumption of analgesics. It can be explained by causing lysis of oral bacteria's and helping to reduce bacterial load in all areas prone to mucositis. The results showed patients in intervention group has delayed mucositis and less used of analgesic as compared to placebo group.[6,8]

It is suggested that essential oil had the role in improving oral health by causing lysis of oral bacteria and helping to reduce bacterial load.

Essential oils

Essential oils have antibacterial and antifungal effects and these natural compounds have been applied to treat the skin and mucosal infection. *Gravett a*ssessed mixed essential oil as mouth wash for oral mucositis. A combination of Melaeuca alternifolia 1 drop + Citrus bergamail 1 drop + Pelargonium Grraveolens 1 drop with half glass of boiled warm water to gargle 5 times/day. This mouthwash was added to routine care in treatment of oral mucositis as there was less burning sensation, discomfort so patients preferred to use this mouth wash as in comparison to routine mouth wash which was used.

In another study, patients undergoing for chemotherapy randomly divided in to two group placebo and peppermint oil was used. The10 drops of peppermint essential oils 3 times/day as oral rinse reduces the incidence of oral mucositis by 15%.

Peppermint essence is an effective, safe, and well tolerated product for prophylactic treatment of chemo-induced oral mucositis.

RHODIOLA ALGIDA FISCH AND C. A. MEY (STONECROP)

It is a Tibetan plant from *Crassulaceae* family which is used in traditional remedies of Asian and European countries. It contains compounds such as salidroside and polyphenols and are demonstrated to improve the activity of immune system. In a trial of breast cancer patients were administered with *Rhodiola algida* extract of placebo after 2 weeks patient in intervention group has significantly lower pain and fewer number of ulcers in oral cavity, and even shorter period of ulcers too.

SALVADORAPERSICA

Miswak it is most widely used chewing stick in middle east country. It accelerates healing of ulceration induced by ethanol, endomethasone in animal studies, it was found that it was effective in reducing incidence of oral mucositis in animal studies. It provides good oral hygiene and level of KGF will also be high in mucosa.[8]

Ziziphus Jujuba

It is herb that is widely distributed in Europe and Asia the main active constituents in herb are cyclopeptide alkaloids, flavonoids, sterols, jujubosides A, jujuboside B, Lauric acid, and triterpenoid and saponins. Topical and systemic form of hydroalcoholic extract was associated with reduced intensity of oral mucositis. Anti-inflammatory properties of herbs are useful in prevention and management of oral mucositis.

Korean red ginseng

It can be used as an additive material in small doses in additive form in tea, or coffee, it have been used in cases of radiation induced oropharyeangeal mucositis.[5]

Human placenta

Human placental extract contains a complex mixture of different material such as polyribonucleotide, RNA, DNA, peptides, aminoacids, enzymes, and other scarce ingredients. These products have anti-inflammatory functions and it can be used as preventive and curative measure for chemo, radio-induced mucositis. Recent studies have demonstrated that placentrex stimulates the pituitary and the adrenal cortex and normalize the tissue metabolism. It also increases the vascularity of the tissues. In clinical trial of cancer patients under radiation therapy received placental treatment and normal prescribed treatment. Placentirix was given as 2 ml IM injection 5 days/week for 3 weeks the control group received aspirin gargle and betamethasone oral drops, decrease in pain in 80% of the cases in placentrex group and 36.7% in control group. Progress in grade 3 mucositis was also less in placentrex group that was 40% and in control group it was 86.7%.there was also improvement in swallowing.

The anti-inflammatory effect of placentrex is due to membrane stabilization and reduction of adenosine triphosphate synthesis. The circadian rhythm al so affect the cell cycle of normal mucosa which can result in grade 3 and grade 4 mucositis, the most sensitive phase of the cycle of oral mucosa to irradiation are G2and M phase based on this radiotherapy in morning is better than in evening, it will also results in less mucositis.[8]

Honey and bee products

Honey has been used for management of oral mucositis. *Golder* indicated that propolis is beneficial for the treatment of mucositis induced by radiation therapy. The effect of propolis on radiation-induced mucositis is beneficial.[8]

Honey has been used for dressing surgical wounds, and burn cases. Honey is also used for the prevention and management of oral mucositis. It has anti-bacterial, antifungal and analgesic effects. It also helps in the re-epithelialization. Honey was used by Vibha Singh *et al*. in the management of radiation-induced mucositis and showed drastic improvement in terms of quality of life after 3 weeks, Recovery was faster that control group. 20 ml of honey was given to

patient 15 min prior to radiation was followed by maximum 100 ml/day till the radiation treatment. The result was quite promising in term of quality of life.

The reduction in pain by honey is through blocking exposure of the damaged mucosa to the oxygen so tissue oxygenation will be postponed. The wound healing effect is because of viscosity acidic pH which will be effective in inhibiting bacterial growth on mucosa. It also inhibit hydrogen peroxide converted from glucose oxidase and gluconic acid and enzymes which probably are the growth factors and nutritive minerals and vitamins that helps repair the tissue directly. Honey is not generic drug so description of honey is not easy. The component depends upon flora of the region from where the honey has been collected. It contains more than 20% water, vitamin, enzymes protein, and high concentrated sugar invertase, diastase, and glucose oxidase are the honey enzymes.

Honey reduces wound pain by postponing tissue oxygenation through blocking exposure of the damaged mucosa to oxygen. Biswal suggested that effectiveness of honey on wound healing might be because of the hygroscopic nature of the honey its viscosity, its acidic pH which prevents bacteria to grow on the mucosa inhibit hydrogen peroxide converted from glucose oxidase and gluconic acid, enzymes which probably are growth factors and tissue nutritive minerals and vitamins that help repair the tissue directly.

The use of honey can results in more caries but proper oral hygiene should be marinated. It is not clear the antimicrobial activity of honey is its result of its delays of hydrogen peroxide on exposure to catalase or the result of its high osmolarity.[8]

Benzydamine hydrochloride

It is a non-steroid drug that has exhibited local anti-inflammatory, analgesic, anesthetic, and antimicrobial activities, based on several clinical studies topical benzydamine is effective in radiation induced oral mucositis.

ANTIULCER DRUGS

Sucralfate

It is a basic aluminum salt of sucrose sulfate (sulfated disaccharide) generally used as therapeutic agent in patient with peptic ulcer, on ulcerated mucosa it produces paste like protective coat the local production of prostaglandin improved, and there is increase in interlukin-1 and interlukin-2 release from fibroblast. Its anti-inflammatory effect is also effective in topical application.

Prostaglandins

The mucosal application of prostaglandin E-2 has shown cytoprotective effect in peptic ulcers Its effect as a cyto-protective agent has also been observed in oral mucositis.

Growth factors

Growth factors are effective in impaired wound healing. Granulocyte/Macrophage Colony Stimulating Factor (GM-CSF) and G-CSF are effective in increasing keratinocyte and fibroblast growth.

Epidermal growth factor

Epidermal growth factor (EGF) is stimulated cell growth, proliferation and differentiation by binding to its receptor EGFR. EGF leads to the proliferation of cells. It is given as oral aerosol and may have benefit in chemoradio-induced mucositis in head and neck cancer.

Keratinocyte growth factor

It is also known as keratinocyte growth factor present in epithelialization phase of wound healing, keratinocytes are covering the wound and can help forming the epithelium so this activity may be helpful in tissue repair can be used in chemo radio induced mucositis.

ANTIMICROBIAL DRUGS

Any damage to oral mucosa may lead to infection, as there will be hyposalivation leads to decrease IgA this may allow bacteria to regrow bacterial lying in upper respiratory and GI compared to bacteria, and fungi, viral infection in oral cavity looks to be less clinical complication during radiotherapy.

Glutamine

It is one of the 20 amino acids encoded by standard genetic code, it is also used by cells of the immune system such as lymphocytes and macrophages.[14]

It is amino acid which is used by cells of immune system such as lymphocytes and macrophages. Some clinical studies say dietary supplements with glutamine may protect gut from side effects.

Vitamin E

Alfa tocopherol is antioxidants which may protect tissue damage from free oxygen radicals during radiation therapy.

Calcium phosphate

Inorganic and organic phosphate both in extracellular and intracellular ways can affect mucosal surface and may improve mucositis.[14]

Traumeel S

Homeopathic medication, it is used in form of mouth wash was used in stem cell allogenic and autologous stem cell transplantation. This study was found that Traumeel S may reduce significantly the severity and duration of the chemotherapy induced mucositis.

In chemo-induced mucositis homeopathic medicine plays very important role, it reduces severity of mucositis.

DISCUSSION

The herbal medicines have anti-inflammatory, antioxidants, antiseptic, sedative, and wound healing properties. Their role in the management of oral mucositis is based on above properties.

Anti-inflammatory properties of herbs are useful in prevention and management of oral mucositis as induction of pro-inflammatory cytokines such as TNF–(alfa) , interlukin 1 beta and IL-6 plays important role in amplification or tissue injury through activation of NF-Kbeta and matrix metalloproteinase targeting their pro-inflammatory cytokines may be an important part of some medicinal plants such as Chamomile and *Hippophae Rhamnoides*, which reduce the tissue level of IL-1 beta and TNF-2.

The role of honey as an anti-inflammatory is proven. It inhibits prostaglandin level in both plasma and mucosal tissues.[8,9]

Analgesic effects

Some medicinal herbs have analgesic effects which are very important in ulcerative forms of mucositis. For instance, ginger extract contains analgesic compounds namely gingerol and shogaol which have analgesic effects.

Growth factors

Healing process is initiated by signaling pathways that r\ target proliferation and differentiation of epithelial cells. The most promising growth factors that regulate growth and proliferation of epithelial cells in fibroblast growth factors (KGF). It is most potent growth factor that induces epithelial growth and proliferation. Palifermin the generic name of the KGF is the first compound approved by FDA to reduce mucositis.[15]

ORAL HYGIENE

Oral hygiene plays a very important role in patients receiving chemotherapy.[13]

Laser therapy is very effective in the treatment of radiotherapy-and chemotherapy-induced oral mucositis. It is suggested that the release of endorphins may be involved in alleviating pain and that fibroblast transformation to myofibroblast can increase wound healing. Radiation can also damage tissue, leading to inflammation, infection and osteoradionecrosis. Preventive measures which can be taken to minimize these complications include well-balanced diet, minimizing the use of removable dentures or devices and prevention of smoking and alcohol, intake. Topical application of antibiotics and pain killers should be prescribed. Hyperbaric oxygen therapy should be used in the case of delayed healing.

There is no universally accepted pre-cancer therapy dental protocol. However, daily brushing, oral rinsing with saline and warm water is recommended. Oral rinse with alcoholic content should be avoided. Toothpastes with whitening agent should be avoided, and so should the use of vaseline-based agents for moisturization. If the platelet count is <40,000, flossing should be avoided. Fluid intake should be optimum. Chlorhexidine should be avoided in cases of solid tumor.

There are mucosal protect ants such as Gelclair and Zilactinwhich work by coating mucosa on exposed nerve endings so that patients can have food and tongue mobility for eating and speaking.

There is another FDA approved agent named Amifostine, which offers protection against damage to mucosa during radiation therapy.

There are some other organic agents are available like Capsicin (derived from chilli preparations), Vitamin E, Sucralfate, and Allopurinol mouth wash, which are used with some degree of success.

In a study By Zin Xiang, they reported use of Dioctahedral Smectite in comparison to Iodine Glycerine cream. They found that DSIG cream significantly reduced OM duration and symptoms. It should not be used in patients with radiotherapy. It is natural adsorbent clay formed of aluminum magnesium silicate and is efficient in protection against gastrointestinal mucosa. It reduces microbes, enhances the intestinal barrier and prevents mucosal damage.

There are antiseptic topical solutions which contains iodine, like Gention violet and Silver coordinated polymers which also effective in the treatment of oral ulcer and have a strong antimicrobial action. The mucoprotective action of DSIG might be attributed to its barrier function due to unbalanced charge distribution. It can specifically bind strain *E. coli*. It also act as a barrier by shielding the OM from bacterial and

fungi invasiveness, and releasing pro-inflammatory cytokines to repair the damage mucosa.

The iodine glycerine is effective in inhibiting bacteria and fungi specially C. Albicans.

There are studies reported that Vitamin B 12 plus Gentamycin might be useful in prevention and relieve pain and promote repair. There are also reports which claim that 100 MG Vitamin E twice a day may be effective in repairing oral mucositis.[16]

There are certain patient education points which can minimize patients discomfort after having mucositis.

Patients should ask to sit in upright position and lean their head forward. Eating should be at a slower pace and fruits should be cut in small pieces. Small meals should be taken instead of large, heavy meals. Hot food should be avoided and food at room temperature should be preferred. Soft food should be taken and crunchy food should be avoided. Straws should be used to make drinking easy and to avoid direct contact with mucosa to reduce patients discomfort. Talking during eating should be avoided. Acidic foods like grapes, tomatoes, alcohol, tobacco, and spicy food should be avoided.

CONCLUSION

Mucositis is a side effect of cancer therapy.

Many studies have generated good evidence for Ayurvedic and plant-based interventions in prevention of radiation induces mucositis. Nowadays, a standard preventive agent for mucositis is not available from natural products, with well documented several multicenter clinical trails. Properly designed clinical trials to prove efficacy of herbal agents for controlling radio chemo induced oral mucositis is required. Natural products have potential to reduce oral mucositis. These include honey, volatile oils, Nagilla sativa, and Tulsi, which are known and have scientifically proven radio-protective properties as well as antioxidant properties too. The treatment needs to be discontinued in some patients owing to non-tolerance to therapy. Thus, there is need for some non-invasive and preventive measures for mucositis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol 2009;45:1015-20.
2. Noor Al Dasooqi Stephen TS, Stephen T Sonis, Joanne M Bowen, Emma Bateman, Nicole Balijlevens, *et al*. Emerging evidence on the pathobiology of mucositis .Support Care Cancer 2013;21;3233-241.
3. Raber-Durlacher JE, Elad S, Barasch A. Oral mucositis. Oral Oncol 2010;46:452-6.
4. Yarom N, Hovan A, Paolo B, Ariyawardana A, Jensen SB, Gobbo M *et al.* Systemic review of natural and miscellaneous for management of oral mucositis in cancer patients and clinical practice guidelines Part -1 Vitamins, minerals and nutritional supplements. Supportive Care Cancer 2019;27;3997-4010.
5. Moslemi D, Nokhandani AM, Otaghsaraei MT, Moghadamnia Y, Kazemi S, Moghadamnia AA. Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature. Radiother Oncol 2016;120:13-20. doi: 10.1016/j.radonc.2016.04.001. Epub 2016 Apr 21. PMID: 27113797.
6. Bahramsoltani R. Medicinal plants for chemoradiotherapy-induced oral mucositis: A review of clinical studies. Trad Integr Med 2017;2:196-207.
7. Yarom N, Ariyawardana A, Hovan A, Barasch A, Jarvis V, Jensen SB, *et al*. Systematic review of natural agents for the management of oral mucositis in cancer patients. Support Care Cancer 2013;21:3209-21.
8. Zakaria S. Natural remedies target different therapeutic pathways in oral mucositis induced by cancer chemo or radiotherapy. Am J Phytomed Clin Therap 2017;5:4.
9. Moslemi D, Mohammadi Akram Mohammadi Nokhandani, MahsaTaheriOtaghsaraei Yasaman Moghadamnia Sohrab Kazemi, AlliAkbar Moghadamnia. Management of chemo/radiation induced oral mucositis in patients with head and neck cancer a review of current literature. Radiother Oncol 2016;120:13-20.
10. Baharvand M, Jafari S, Mortazavi H. Herbs in oral mucositis. J Clin Dianostic Res 2017;11:5-11.
11. Azar Aghamohmmadi MS, Hosseinimehr SJ. Natural products for management of oral mucositis induced by radiotherapy and chemotherapy. Intergrative Cancer Ther 2016;15:60-8.
12. Rebecca Stone Monica C, Flidner A, Ntonie CM. Smiet mangement of oral mucositis in patient with cancer. European Journal of Oncology Nursing 9 Suppl 1:S24-32 DOI: 10.1016/j.ejon.2005.08.004.
13. Hitomi S, Ujihara I, Sago-Ito M, Nodai T, Shikayama T, Inenaga K, *et al*. Hyposalivation due to chemotherapy exacerbates oral ulcerative mucositis and delays its healing. Arch Oral Biol 2019;105:20-6.
14. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, *et al*. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120:1453-61.
15. Oronsky B, Goyal S, Kim MM, Cabrales P, Lybeck M, Caroen S, *et al*. A review of clinical radioprotection and chemoprotection for oral mucositis. Transl Oncol 2018;11:771-8.
16. Lin JX, Fan ZY, Lin Q, Wu DH, Wu XY, Chen YR, *et al*. A comparison of dioctahedral smectite and iodine glycerin cream with topical mouth rinse in treatment of chemotherapy induced oral mucositis: A pilot study. Eur J Oncol Nurs. 2015;19:136-41. doi: 10.1016/j.ejon.2014.10.006. Epub 2014 Nov 18. PMID: 25465773.
17. Bowen J, N Al Dasooqi, P Bossi, H Wardill, Y Van Sebille, AAl-Azri. The pathogenesis of mucositsi – Updated perspectives and emerging targets. Supportive Care Cancer 2019;27:4023 33.
18. Hamme GM, Beckmann K, Radtke J, Efferth T, Greten HJ, Rostock M, Schroder S. A survey of chinese medicinal herbal treatment for chemotherapy-induced oral mucositis. Evidence Based Commplementary Alternative 2013;1-16. https://doi.org/10.1155/2013/284959.
19. Naidu MU, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis-complicating the treatment of cancer. Neoplasia 2004;6:423-31.