REVIEW ARTICLE

A Narrative Review of Herbal Medications in the Management of Mucositis in Head and Neck Cancer Patients

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ABSTRACT

Head and Neck Cancers are generally treated with a combination of surgery, radiotherapy and chemotherapy. These patients inevitably suffer from oropharyngeal mucositis accompanied by xerostomia and salivary alterations like reduced buffering capacity, lowered pH, increased viscosity. These result in severe discomfort to the patients along with lowered quality of life on account of having pain, severe burning sensation, difficulty in day to day activities like speech, mastication, taste and swallowing. Till date various therapeutic agents have been tried for the management of radiotherapy and chemotherapy induced mucositis with partial success. As of now there is no standardized protocol which is being practiced throughout the world for managing this debilitating condition. There has also been a concern among the growing crowd of vegan population who would like to use only herbal products for themselves. This paper has tried to identify the herbal products which need to be investigated better. Future work using larger sample size and proper randomization is necessary for establishing a standardized protocol across the world and generalization of their applicability.

Keywords: Herbal, Oral Mucositis, Radiation Mucositis, Head & Neck cancers, Quality of Life

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INTRODUCTION

Radiation mucositis affecting the oropharyngeal region is one of the most common, debilitating, clinical side effects of radiotherapy or chemotherapy used in the management of head and neck cancers. This is usually the initial symptom seen in approximately ninety percent of patients who receive chemo radiation therapy. It presents as a severely incapacitating damage of oral mucosa which occurs as a result of the cancer treatment (1,2). It is characterized by features like inflammation, erythema, ulceration, and pseudo membrane formation and heals in around 2 months after the radiotherapy is completed with atrophic changes.

Patients receiving radiotherapy, more than 2000cGy or concomitant chemotherapy are most likely to develop radiation mucositis (3). One of the major factors influencing onset of Oral Mucositis (OM) is oxidative stress induced by release of inflammatory cytokines (3,4). Dysplastic cells involving those with a high rate of mitosis and a rapid turnover are particularly affected by the radiation energy (5).

WHO scale of OM toxicity is extensively used in regular radiotherapy protocols as it is simple and straightforward tool for assessment and quantification of OM (Table I). This has been deployed rather in majority of researches concerned with this type of methodical appraisal. Patients with Grade 3 as well as Grade 4 OM present with severe oropharyngeal mucositis associated with ulceration and a severe burning sensation badly affecting the patient’s quality of life. This may make it mandatory to necessitate interruption of subsequent doses, decreasing the subsequent doses or even stoppage of intended radiotherapy delivery.

Table I: Grading of Oral Mucositis (World Health Organization)

<table>
<thead>
<tr>
<th>Explanation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>No changes</td>
<td>0</td>
</tr>
<tr>
<td>Soreness ± Erythema</td>
<td>1</td>
</tr>
<tr>
<td>Erythema, ulcers, patients can swallow solid food</td>
<td>2</td>
</tr>
<tr>
<td>Ulcers with extensive erythema, patients cannot swallow solid food</td>
<td>3</td>
</tr>
<tr>
<td>Mucositis to the extent that oral alimentation is not possible</td>
<td>4</td>
</tr>
</tbody>
</table>

It is imperative to put an end to the discomfort associated with mucositis as well as to enhance the nutritional status, and to improve the quality of life so as to enhance the prognosis of the cancer. The range of therapeutic agents available for management of radiation induced damage for oral health care, as of now not very satisfactory. A universally acceptable and totally effective protocol is yet to be evolved.
A wide range of natural agents like aloe vera, honey, curcumin, olive oil has been tried with the aim of identifying a more effective agent to reduce the morbidity. This is done along with ensuring lesser amount of adverse reactions which are usually associated with the chemically derived medicines. Furthermore, they are easily available as most of them are natural herbal products. They are usually sold at supermarkets and grocery stores and obviously are sold without any prescriptions and in medical shops dealing with ayurvedic products often sold without a prescription based on symptoms. Thus these offer a wider scope of their usage by the patients without much of scientific process (4,7).

There has been a steadily increasing population of people across the worlds who are vegans who do not consume a substance if it is not purely of plant origin. This necessitates the need for identifying purely herbal products or products of purely plant origin which can be effective, beneficial and can be used or consumed by the vegans and non-vegans. This paper is in particular focused on herbal therapeutic agents used in management of radiation mucositis.

MATERIALS AND METHODS

In the process, systematic reviews of scientific texts concerning success of natural agents administered for relief from excruciating discomfort of OM was done. Model of PICO (population, intervention, control, and outcomes) was deployed to identify insertion criterion as well as investigate expressions per involvement. Populace was of sufferers with head and neck cancer, who had developed oral mucositis after chemo &/or radiotherapy. All types of association of natural agents or herbal medications were incorporated. Outcome was based on the lessening of severity of the disease.

As a secondary source, some medical databases like The Cochrane Library, Medline, Google scholar databases and some connected journals were reviewed, and the suitable evidence were selected with heightened accuracy. A total number of 213 records were reviewed preliminarily. Of these, 98 articles were removed due to very close resemblance suggestive of duplication and, then finally 142 records were remaining. After screening, 82 articles were additionally disqualified on basis of lack of sufficient relevance. Afterwards, sixty were identified and processed with full-text papers.

The MeSH terms were used to identify studies done to evaluate the competence of usual agents. They were “head and neck cancer”, “herbal medications”, “radiation mucositis”, “xerostomia” and “radiotherapy”. Systematically organized studies along with randomized clinical trials, and all related studies were included in this research. Research papers were selected which were published as full papers in English. The Prisma

RESULTS

For this section, a total of 240 text were analyzed. There were 98 cases which were disqualified because of the similarity and copying and subsequently, 142 reports were sustained. About 82 superfluous disparate data were deleted after the viewing of the record (Table II).

Risk Factors for Oropharyngeal Mucositis

The oral and the pharyngeal mucosa are among the most responsive tissues for complications associated with chemotherapy and radiation therapy. Eighty percent of patients with cancer of head and neck are subjected to radiotherapy. Approximately fifteen percent of patients receiving radiotherapy in the head and neck region needed to be admitted to the hospital for management of radiotherapy associated complications (21,22).

Factors influencing the occurrence of radiation mucositis include oral hygiene status before and throughout the treatment period, mode of radiotherapy, radiotherapy dose, duration of radiotherapy, types of fields used, use of lead lined stents, use of radioprotectors or radiation mitigators, hemoglobin level and blood oxygenation, salivary gland functioning, staging of the malignancy, histopathologic nature of the malignancy, the nutritional status, dietary habits and dietary intake of the patient, renal function, hepatic function and the chemotherapy drugs concurrently prescribed (23,24). Almost forty to seventy percent of patients getting typical chemotherapy regimens are probable likely to contribute to the development of mucositis (25,26).

Clinical Characteristics of Radiation Mucositis

Radiation Mucositis is basically the inflammatory reaction involving the oropharyngeal mucosa. It typically begins around the end of the second
Various topical agents like Caphosol, Episil, GelClair, and MuGard have been anecdotally used but data on their effectiveness in controlling mucositis-related discomfort are inadequate (28,29). Cryotherapy and sipping of ice chips for thirty minutes preceding to and throughout radiation therapy has been revealed to be of help to efficiently soothe the inflammation and pain associated with radiation therapy. Traditional Chinese Medicine (TCM) contains experimental herbal formulas for curing mouth ulcers which has regularly been used by the Chinese in the management of oral mucositis.

Management of Radiation Mucositis

Extensive work has been done in this genre as there is no globally acceptable standard of treatment for mucositis or its associated discomforts. Approach for curing oral mucositis comprise of anticipatory actions and curative methods (27) (Figure 2).

Enhanced oral cleanliness can be done to diminish the severity of the oral mucositis by eliminating the presence of any local irritants. Conventional NSAIDs (Non-steroidal anti-inflammatory drugs) and Opioid Analgesics are prescribed to reduce the pain and discomfort associated with radiation mucositis (28).

**Table II: Summary of Treatments with Herbal Products for Mucositis in Head and Neck Cancer Patients**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Herbal Product</th>
<th>Type of use</th>
<th>No.of Patients</th>
<th>Treatment</th>
<th>Results</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aloe vera</td>
<td>Oral juice</td>
<td>61</td>
<td>RT</td>
<td>Significant reduction in freq of mucositis</td>
<td>Puataweepong P et al. 2009 (8)</td>
</tr>
<tr>
<td>2</td>
<td>Calendula officinalis</td>
<td>Topical mouthwash</td>
<td>40</td>
<td>CT-RT</td>
<td>Significantly decreased intensity of mucositis</td>
<td>Neda Babaei et al. 2013 (9)</td>
</tr>
<tr>
<td>3</td>
<td>Olive leaf extract</td>
<td>Topical mouthwash</td>
<td>25</td>
<td>CT</td>
<td>Significantly decreased intensity of mucositis</td>
<td>Ahmed KM 2013 (10)</td>
</tr>
<tr>
<td>4</td>
<td>Curcuma longa</td>
<td>Topical mouthwash</td>
<td>80</td>
<td>CT-RT</td>
<td>Reduction in the WHO, OMAS, and VAS scores</td>
<td>Rao Suresh et al. 2014 (11)</td>
</tr>
<tr>
<td>5</td>
<td>Matricaria recutita</td>
<td>Topical mouthwash</td>
<td>52</td>
<td>CT</td>
<td>Significant reduction in freq. of mucositis</td>
<td>Renani HA et al. 2012 (12)</td>
</tr>
<tr>
<td>6</td>
<td>Matricaria recutita</td>
<td>Topical mouthwash</td>
<td>1</td>
<td>CT</td>
<td>(case report) Treated case</td>
<td>Mazokopakis E et al. 2005 (13)</td>
</tr>
<tr>
<td>7</td>
<td>Matricaria recutita</td>
<td>Topical mouthwash</td>
<td>40</td>
<td>RT</td>
<td>Reduced incidence, intensity &amp; duration of mucositis</td>
<td>Fernanda T.M.M. Braga et al. 2015 (14)</td>
</tr>
<tr>
<td>8</td>
<td>Matricaria recutita</td>
<td>Topical mouthwash</td>
<td>164</td>
<td>CT</td>
<td>No difference in freq of mucositis</td>
<td>Fidler P et al. 1996 (15)</td>
</tr>
<tr>
<td>9</td>
<td>Glycyrrhia glabra</td>
<td>Topical mouthwash</td>
<td>45</td>
<td>RT</td>
<td>Result showed better outcome for mucositis</td>
<td>Ismail AA Ismail AA et al. 2004 (16)</td>
</tr>
<tr>
<td>10</td>
<td>Peppermint</td>
<td>Topical mouthwash</td>
<td>40</td>
<td>CT</td>
<td>Significant reduction in freq of mucositis</td>
<td>Ashktorab T et al. 2010 (17)</td>
</tr>
<tr>
<td>11</td>
<td>Chamomile</td>
<td>Topical mouthwash</td>
<td>60</td>
<td>CT</td>
<td>Significant reduction in freq of mucositis</td>
<td>Abd Elwadoud AM et al. 2019 (18)</td>
</tr>
<tr>
<td>12</td>
<td>Indigo wood root</td>
<td>Topical mouthwash</td>
<td>20</td>
<td>RT</td>
<td>Reduction in severity of mucositis, anorexia, dysphagia</td>
<td>You WC et al. 2009 (19)</td>
</tr>
<tr>
<td>13</td>
<td>Turmeric</td>
<td>Topical mouthwash</td>
<td>80</td>
<td>CT-RT</td>
<td>Reduced incidence of mucositis, less weight loss</td>
<td>Rao Suresh et al. 2014 (20)</td>
</tr>
</tbody>
</table>

Abbreviations: OMAS, Oral Mucositis Assessment Scale; VAS, Visual Analog Pain Scale; WHO, World Health Organization; RT, radiotherapy; CT, chemotherapy.

Various topical agents like Caphosol, Episil, GelClair, and MuGard have been anecdotally used but data on their effectiveness in controlling mucositis-related discomfort are inadequate (28,29). Cryotherapy and sipping of ice chips for thirty minutes preceding to and throughout radiation therapy has been revealed to be of help to efficiently soothe the inflammation and pain associated with radiation therapy. Traditional Chinese Medicine (TCM) contains experimental herbal formulas for curing mouth ulcers which has regularly been used by the Chinese in the management of oral mucositis.

**Figure 2: Strategies for Managing Oral Mucositis**
and (37). However, lack of suitable randomized controlled trials and non-availability of these Chinese herbs in other parts of the world has rendered any consideration for their use as non-feasible. In the western part of the world, several herbal medicinal plants exist like Salvia officinalis, Matriciana camomilla, Hamamelis virginiana, Potentilla recta, Commiphora molmol, Althaea spps, Malva spps, Cetraria islandica, Linum usitatissimum, Myrtillus truncus, Hippophae rhamnoides, Aloe vera, Carica papaya, Centaurii herba, Gentianae radix, Menyanthes folium, Eriodictyon crassifolium, Oleum olivae and Citrus limon. Of these, Matriciana camomilla, Chimonanthus salicifolius and Aloe vera have been used in some of the studies with a partial relief reported in some of them (2, 14, 21, 31, 32). Curcumin, a polyphenol isolated from the rhizome of Curcuma longa, has antioxidant, antimicrobial, and anti-inflammatory properties (33).

**DISCUSSION**

Energy of radiotherapy is partially absorbed by the oral mucosal cells which results in the development of a debilitating situation identified as oral mucositis (34). This condition begins as a mild erythematous appearance associated with burning sensation which progresses to ulceration and finally pseudomembrane formation. Patients find it difficult to masticate or ingest as a result of oral mucositis (35). It has an adverse effect on the treatment plan and prognosis of the illness, effecting the efficiency of radiotherapy (36). It has also been experimentally found that the aqueous extract of the betel nut is a potent carcinogen to mouse kidney cells in vitro (37). The fundamental treatment of oral mucositis is intended to alleviate discomfort and uneasiness related with it (38).

The search for ideal “herbal” and “natural” cure for a variety of signs has been steadily mounting throughout the last few decades largely due to the notion that they are completely safe. Most of such agents are inadequately studied and often accessible without a prescription. These cures can sometimes be associated with serious health perils (39). Curcumin, an herbal agent present in Indian spice ‘Turmeric’ has anti-inflammatory, immunomodulation and wound healing properties (40). Caffeic acid phenyl ethyl ester (CAPE) is a brawny antioxidant which can put off the proliferation of neoplastic cells (17, 34). Basil is a significant medicinal with antioxidant, anti-inflammatory properties, Yashhi-Madhu (Glycyrrhiza glabra) has of late acquired meaning (42). Peppermint spirit (PE) can lessen the side effects of cancer conduct (22).

Chamomile is made up of coumarins, flavonoids, terpenoids and alpha-bisabolol and chamazulene. Dos Reis et al. accounted that Chamomile has constructive resultson oral mucositis wounds (39). Researchers have shown inconsistent data on the healing effect of vitamins on mucositis (43).

Aloe vera has been consumed traditionally to aid with healing of injuries and has been used to care for radiation induced dermatitis (44). Many researchers have also indicated that turmeric and its constituent curcumin have anti-inflammatory property, promote reepithelialization, and improve healing of wounds generated as a result of exposure to radiation (45, 46). These findings are suggestive of the valuable healing aspects of turmeric in management of radiation induced mucositis. Cruz (46) published report of a single blinded randomized control trial (RCT) using Virgin Coconut Oil in patients with nasopharyngeal neoplasms with a reduction of grade 2 and above radiation-induced mucositis. This has led to the reduction in incidence rate of mucositis, delay in onset of development of grade 2 and above radiation-induced mucositis and decreased toxicity suggestive that this maybe a useful adjunct in the management of radiation induced mucositis.

**CONCLUSION**

Head and neck cancer patients undergoing radiotherapy inevitably suffer from radiation induced oral mucositis, which adversely affects their quality of life. Inflammatory mediators and ROS (Reactive oxygen species) are cellular level molecules closely correlated to mucositis. It is truly heartening to observe that agony of mucositis in head and neck cancer patients can be reduced to a great degree by usage of naturally occurring herbal preparations. In order to develop better standardized protocols which can effectively prevent and heal the oropharyngeal mucositis and lessen their associated discomfort and agony, well designed multicentric RCT sare required to identify and establish the ideal herbal drugs.

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