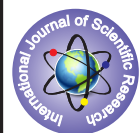


THE EFFECT OF HONEY ON MUCOSITIS INDUCED BY CHEMO-RADIATION IN HEAD AND NECK CANCER



Medical Science

KEYWORDS: Mucositis, Buccal Cavity, Lubricants, Epithelial tissues.

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ABSTRACT

Mucositis is inflammation of buccal cavity, it is common complication of chemo and radiation therapy in head and neck cancer patients. This reduces the food intake capacity of the patients and also adds in pain and other health complications as post treatment .Honey has natural anti infective and soothing capacity. The present work assessed the use of honey for the treatment of radiation induced mucositis .

Introduction-Mucositis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemo therapy and radiotherapy treatment for cancer. Mucositis can occur anywhere along the gastrointestinal (GI) tract, but oral mucositis refers to the particular inflammation and ulceration that occurs in the mouth. Oral mucositis is a common and often debilitating complication of cancer treatment.

For most cancer treatment, about 5-15% of patients get mucositis. However, with 5-treatment with fluorouracil (5-FU), up to 40% of the patients get mucositis, and 10-15% get grade 3-4 oral mucositis. Treatment with Irinotecan is associated with severe GI mucositis in over 20% of patients also 75-85% of bone marrow transplantation recipients experience mucositis, of which oral mucositis is the most common and most debilitating, especially when melphalan is used in the curative regime. In grade 3 oral mucositis, the patient is unable to eat solid food, and in grade 4, the patient is unable to consume liquids as well.

Radiotherapy to the head and neck or to the pelvis or abdomen is associated with Grade 3 and Grade 4 oral or GI mucositis, respectively, often exceeding 50% of patients. Among patients undergoing head and neck radiotherapy, pain and decreased oral function may persist long after the conclusion of therapy. Fractionated radiation dosage increases the risk of mucositis to > 70% of patients in most trials. Oral mucositis is particularly profound and prolonged among HSCT recipients who receive total body irradiation. Mucositis occurs when cancer treatments break down the rapidly divided epithelial cells lining the gastro-intestinal tract (which goes from the mouth to the anus), leaving the mucosal tissue open to ulceration and infection. Mucosal tissue, also known as mucosa or the mucous membrane, lines all body passages that communicate with the air, such as the respiratory and alimentary tracts, and have cells and associated glands that secrete mucus. The part of this lining that covers the mouth, called the oral mucosa, is one of the most sensitive parts of the body and is particularly vulnerable to chemotherapy and radiation. The oral cavity is the most common location for mucositis.

Oral mucositis is probably the most common, debilitating complication of cancer treatments, particularly chemotherapy and radiation. It can lead to several problems, including pain, nutritional problems as a result of inability to eat, and increased risk of infection due to open sores in the mucosa. It has a significant effect on the patient's quality of life and can be dose-limiting (i.e., requiring a reduction in subsequent chemotherapy doses).

Signs and symptoms of mucositis include:

- Red, shiny, or swollen mouth and gums
- Blood in the mouth
- Sores in the mouth or on the gums or tongue
- Soreness or pain in the mouth or throat
- Difficulty swallowing or talking
- Feeling of dryness, mild burning, or pain when eating food

- Soft, whitish patches or pus in the mouth or on the tongue
- Increased mucus or thicker saliva in the mouth

An extreme case of the condition is called confluent mucositis. In a worst case, the mucous membrane of the patient's entire mouth and tongue can be coated by a white mucus coating that is up to a millimeter thick. The combination of mucus, excess saliva and pain can make it difficult or even impossible to eat. When caused by chemotherapy, mucositis is usually due to the low white blood cell count; when caused by radiation, mucositis is usually due to the necrotic and inflammatory effect of radiation energy on oral mucosa.

-Chronic irritation from ill-fitting prostheses or faulty restorations can predispose patients to the development of oral mucositis due to local irritation and trauma.

-Generally, patients with hematologic malignancies have an increased rate of oral mucositis compared with those with solid tumors. This is to some extent related to the treatment regimens.

-Hyposalivation prior to and during treatment is associated with an increased risk of oral mucositis.

-The use of methotrexate for chronic GVHD prophylaxis may exacerbate lesions of oral mucositis, although this is less of a concern with newer prophylaxis regimens.

-Oral mucositis occurs independently of oral mucosal infections of viral and fungal etiology, but it may be exacerbated by such concomitant infections.

Younger patients tend to develop oral mucositis more often than older patients being treated for the same malignancy with the same regimen. This appears to be due to the more rapid rate of basal cell turnover noted in children. However, the healing of oral mucositis is also more rapid in the younger age group. It is important that cancer patients be on the lookout for signs of mucositis, which should be treated as soon as possible once diagnosed. The consequences of mucositis can be mild, requiring little intervention, but they can also be severe--such as hypovolemia, electrolyte abnormalities, and malnutrition and even result in fatality. Oral mucositis can:

- Cause pain
- Restrict oral intake
- Act as a portal of entry for organisms
- Contribute to interruption of therapy
- Increase the use of antibiotics and narcotics
- Increase the length of hospitalization
- Increase the overall cost of treatment.

Patients with oral mucositis and neutropenia (a type of white blood cell deficiency) have a relative risk of septicemia (a systemic, toxic illness caused by the invasion of the bloodstream by virulent bacteria coming from a local infection) more than 4 times that of patients with

neutropenia only. Mucositis is further complicated by the nausea and vomiting that often occurs with treatment. Chemotherapy and radiation therapy can affect the ability of cells to reproduce, slowing healing of the oral mucosa, often extending the duration of present mucositis. Patients with damaged oral mucosa and reduced immunity are also prone to mouth infections.

Oral mucositis generally begins 5-10 days following the initiation of chemotherapy and lasts anywhere from one week to six weeks or more. Resolution (in the case of HCT) coincides with recovery of the white blood cell count, specifically when the absolute neutrophil count becomes greater than 500 cells/ μ L. In patients being treated for solid tumors, the duration of oral mucositis depends on the type, dose, and course of treatment.

Honey is a sweet food made by bees foraging nectar from flowers. The variety produced by honey bees (the genus *Apis*) is the one most commonly referred to, as it is the type of honey collected by most beekeepers and consumed by people. Honey is also produced by bumblebees, stingless bees, and other hymenopteran insects such as honey wasps, though the quantity is generally lower and they have slightly different properties compared to honey from the genus *Apis*. Honey bees convert nectar into honey by a process of regurgitation and evaporation: they store it as a primary food source in wax honeycombs inside the beehive. Mucositis, pain and dysphagia are the most distressing symptoms among patients treated with radiation in head and neck region. Concomitant chemotherapy aggravates this toxicity and interruption of treatment becomes unavoidable during a 6 week course of chemoradiation. Currently, studies are attempting to find newer agents that are effective, safe easy to use and inexpensive. Pure honey is an agent which holds promise.

Honey gets its sweetness from the mono-saccharides fructose and glucose, and has about the same relative sweetness as granulated sugar. It has attractive chemical properties for baking and a distinctive flavor that leads some people to prefer it to sugar and other sweeteners. Most microorganisms do not grow in honey so sealed honey does not spoil, even after thousands of years. Some previous studies show that honey has good oral sore healing capacity and great buccal mucosa's atrophy reduction was observed.

Thus this research was designed to assess the healing capacity of natural pure ,grade -A honey on chemotherapy and radiation induced mucositis.

Total 207 patients diagnosed with head neck cancer requiring radiation to the oro-pharyngeal mucosal area were randomly picked by contacting patients registered in Govt Hospitals of Raipur and Bilaspur city and then divided into many groups to receive either chemo radiation plus topical application of honey, mouth rinse, anti-infective agents ,cryo therapy and two therapies together.

Study Area- Raipur and Bilaspur Districts

Study Time- September 2010-December 2012

Patients were treated using a tele-cobalt machine at 2 Gy per day, five times a week up to a total dose of 66 Gy.

In the study arm, patients were advised to take 20 ml of honey 15 minutes before, 15 minutes after and similar amount at bed time. Other groups taking mouth rinse and anti infective agents were given as per prescribed directives.

Patients were evaluated every week for the development/ reduction in severity of radiation mucositis using the WHO grading system.

Grade -I Mucositis



Grade-IV Mucositis



OBSERVATIONS-

TABLE-1
Age Range & site of Cancer of the studies patients

Variables	Age Groups		
Mean Age	25-35	35-40	40-50
Sex			
Male	11	12	13
Female	24	19	26
Site of oral cancer			
Buccal Mucosa	9	8	11
Tongue	7	5	4
Upper alveolus	4	6	8
Lower alveolus	3	--	2
Maxillary antrum	6	3	2
Soft palate	--	6	2
Floor of the mouth	6	3	10
Stage			
Stage I	2	9	7
Stage II	7	5	3
Stage III	5	2	12
Stage IV (a)	4	7	4
Stage IV(b)	8	--	5
Stage IV(c)	9	8	8
Duration of Radio therapy	8.2 weeks	7.6 weeks	8.6 weeks

TABLE-2 Groups of Patients with various therapies

Variables	Gelclair Mouth rinse	Caphosol Oral Lubricant	Glutamine Anti infective	Cryo-therapy	Honey alone	Honey with cryo therapy
Mean Age	35	42	29	31	40	37
Sex						
Male	11	12	13	21	15	16
Female	24	19	26	9	21	20
Site of oral cancer						
Buccle Mucosa	9	8	11	5	8	9
Tongue	7	5	4	5	5	7
Upper alveolus	4	6	8	5	7	--
Lower alveolus	3	--	2	--	5	3
Maxillary antrum	6	3	2	1	1	6
Soft palate	--	6	2	4	3	8
Floor of the mouth	6	3	10	10	7	3
Stage						
Stage I	2	9	7	2	9	8
Stage II	7	5	3	6	2	5
Stage III	5	2	12	9	4	7
Stage IV (a)	4	7	4	8	6	--
Stage IV(b)	8	--	5	4	7	8
Stage IV(c)	9	8	8	1	8	8
Duration of Radio therapy	8.2 weeks	7.6 weeks	8.6 weeks	9.1 weeks	9.3 weeks	8.6 weeks

TABLE-3 Effect of Treatment of Mucositis with various Agents on the severity Level

variables	Gelclair Mouth rinse	Caphosol Oral Lubricant	Glutamine Anti infective	Cryo-therapy	Honey alone	Honey with cryo therapy
Mouth Pain reduction	12%	13%	18%	21%	23%	42%
Mouth sores reduction	9%	10%	9%	11%	24%	22%
Reduction Difficulty in speaking	5%	8%	10%	12%	29%	30%
Reduction in Restricted speaking	8%	10%	4%	14%	39%	40%
Reduction in Difficulty in eating solid foods	4%	5%	8%	6%	21%	19%
Reduction in Difficulty in eating Liquid foods	10%	11%	11%	16%	55%	60%
Reduction in Difficulty in eating hard foods	2%	4%	6%	7%	21%	19%
Reduction in Difficulty in swallowing	6%	6%	4%	10%	21%	19%
Reduction in Change in taste	5%	9%	10%	12%	30%	38%
Reduction in Soreness	2%	6%	6%	8%	48%	44%
Reduction in Erythema	4%	8%	8%	6%	78%	70%
Improvement in Salivation	4%	6%	6%	10%	60%	65%
Reduction in Atrophy	6%	4%	7%	16%	75%	80%
Reduction in edema	5%	6%	10%	18%	80%	75%

TABLE-4

WHO Grading System for Acute Radiation – induced Mucositis	
Grade	Features
0	None
1	Soreness + erythema
2	Erythema, ulcers, and patient can swallow solid food
3	Ulcers with extensive erythema and patient cannot swallow solid food
4	Mucositis to the extent that alimentation is not possible

RESULTS & DISCUSSION-

There was significant reduction in the symptomatic grades 3 and 4 mucositis in honey-treated patients compared to other groups, 18% versus 48% for grade 3 and 4% versus 22% for grade 4 mucositis. The other curative therapies like mouth rinse, oral lubricants, anti infective agents and cryo-therapy was not proved significant to the level of honey. Honey not only significantly reduces the pain, but also corrects the condition of atrophy, edema and erythema. The patients using honey showed better salivation with improvements in liquid and solid material swallowing. The pain and difficulty in speaking was markedly reduced. The combination of honey with cryo therapy also showed good results in many aspects. Honey is a cheap, simple, easily available and effective agent in reducing radiation-induced mucositis. Honey enhances epithelialisation of the mucosa, thereby reducing morbidity.

A similar study on the effect of honey on radiotherapy induced oral mucositis was conducted by Biswal et al. The study showed the efficacy of honey in radiation mucositis, and suggested similar treatment in the management of chemotherapy induced oral stomatitis/mucositis and in mucositis of bone marrow transplant patients.

Within the limits of this study the results showed the application of natural honey is effective in managing radiation induced mucositis, which warrants further multi-centric randomized trials to validate the findings.

REFERENCE

1. Vokes EE, Weichselbann RR, Lipmann S, Hong WK – Head and neck cancer. *N Engl J Med* 1994; 328: 184-94.
2. Biswas LN, Manna B, Sengupta S, Maiti P – Pattern of cancer occurrence in south west region of Bengal : a hospital based study. *J Clin Radiother Oncol* 2002; 2: 24-9.
3. Karmakar R, Bandyopadhyay A, Barui G, Maiti PK, Bhattacharyya A, Choudhury MK – Pattern of cancer occurrence in rural population of West Bengal : a hospital based study. *J Indian Med Assoc* 2010; 108 : 505-8.
4. Epstein JB, Wong FL – The efficacy of sucralfate suspension in the prevention of mucositis due to radiation therapy. *Int J Radiat Oncol Biol Phys* 1994; 28 : 693-8.
5. De Vries A, Sprinzel G, Reich K, Gunczler P, Thumfart W, Lukas P – GM-CSF-mouth wash for treatment of chemotherapy patients with advanced head and neck cancer a clinical trial. *Ann Oncol* 2001; 11: 409PD.
6. Hanson WR, Marks JE, Reddy SP, Simon S, Mihalo WE, Tova Y – Protection from radiation – induced oral mucositis by a mouth rinse containing prostaglandin E1 analogue, misoprostol : a placebo controlled, double blind clinical trial. *Adv Exp Med Biol* 1997; 400 B : 811-8.
7. Leborgne JH, Leborgne F, Zubizarreta E, Ortega B, Mezzer J – Corticosteroids and radiation mucositis in head and neck cancer a double blind placebo-controlled randomized trial. *Radiother Oncol* 1997; 47: 145-8.
8. Tannehill SP, Mehta MP – Amifostine and radiation therapy : past, present and future. *Semin Oncol* 1996; 23 : 69-77.
9. Sonis ST. Oral mucositis in cancer therapy. *J Support Oncol*. 2004;23–8.
10. Bernhoft CH, Skaug N. Oral findings in irradiated edentulous patients. *Int J Oral Surg*. 1985;14:416–27.
11. Motalebnejad M, Akram S, Moghadamnia A, Moulana Z, Omid S. The effect of topical application of pure honey on radiation-induced mucositis: A randomized clinical trial. *J Contemp Dent Pract*. 2008;3:40–4.
12. Biswal 12BM, Zakaria A, Ahmad NM. Topical application of honey in the management of radiation mucositis. *Support Care Cancer*. 2003;11:242–8.
13. Subrahmanyam M. A prospective randomized clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. *Burns*. 1998;24:157–61.
14. Cooper RA, Molan PC, Krishnamoorthy L, Harding KG. Manuka honey used to heal a recalcitrant surgical wound. *Eur J Clin Microbiol Infect Dis*. 2001;20:758–9.
15. Vardi A, Barzilay Z, Linder N, Cohen HA, Paret G, Barzilay A. Local application of honey for treatment of neonatal postoperative wound infection. *Acta Paediatr*. 1998;87:429–32.
16. Vander Weyden EA. The use of honey for the treatment of two patients with pressure ulcers. *Br J Community Nurs*. 2003;8:S14–20.
17. Geneva, Switzerland: World Health Organization; 1979. World Health Organization. Handbook for reporting results of cancer treatment; pp. 15–22.
18. De Vries A, Sprinzel G, Reich K, Gunczler P, Thumfart W, Lukas P. GM-CSF-mouthwash for treatment of chemotherapy patients with advanced head and neck cancer: A clinical trial. *Ann Oncol*. 2001;11:409PD.