Effect of Honey in Radiation Induced Mucositis in Head and Neck Cancer

John Winkle Medida[1], Bala Sankar Ramavath[2], Joseph Benjamin Gandi[3]

ABSTRACT

Introduction: Mucositis is a common side effect of chemo radiotherapy to the head and neck region. It compromises patient's health and quality of life. Standard treatment is not available at present. Care is limited to symptom control. Honey has anti-bacterial and anti-inflammatory properties. It is naturally available, cheap, and ubiquitous. Hence to know the effect of honey in radiation induced mucositis.

Materials & methods: 56 cancer patients receiving concurrent chemoradiotherapy to head and neck region were recruited in this study from October 2012 to august 2014. Study group consisted 27 patients and control group consisted 29 patients. Study group patients received topical application of honey collected from CAROM plant along with chemo radiotherapy and control group patients received only chemo radiotherapy. All patients were assessed twice a week for the onset and severity of mucositis. Both study and control group patients were advised to take plenty of oral fluids, supplementation with high protein diet and oro dental care.

Results: 15 (55.6%) patients in study group developed mucositis at 13th fraction whereas 15(51.7%) patients in control group developed mucositis at 10th fraction indicating that honey postpones the onset of radiation induced mucositis. The severity of radiation induced mucositis at every assessment showed statistically significant difference between study group and control group. This clearly showed control group patients were with higher grades of mucositis than study group patients.

Conclusion: This prospective interventional study found the usefulness of topical application of honey in reducing the onset and severity of radiation induced mucositis in patients receiving chemo radiation to head and neck cancers.

Keywords: Honey, Radiotherapy, mucositis, Head and neck cancers.

INTRODUCTION

The head and neck cancers form the seventh most common cancer worldwide. They are the most common cancers in developing countries, especially in Southeast Asia. Head and neck cancers are more common in males compared to females. This is mainly attributed to the use of tobacco, areca nut, alcohol etc.

Most of the head and neck cancer patients receive radiotherapy at some stage during treatment. Radiotherapy plays a significant role as a primary treatment in early stage and adjuvant treatment later stage head and neck cancers. Due to the radiation-induced DNA damage of surrounding critical structures, radiotherapy can cause debilitating side effects such as skin reactions (erythema, dry desquamation, moist desquamation), oral mucositis (mouth ulceration) xerostomia (dry mouth).

Oral mucositis is caused by a multi-step biological process, which occurs in 30 to 40% of patients receiving chemotherapy, 60% of patients receiving radiation therapy and 92% of patients receiving both chemotherapy and radiation therapy.[1,2,3] It can cause serious secondary complications such as pain, difficulty in eating and swallowing, taste changes, infection, malnutrition and weight loss. It can also lead to a reduction in total dose delivered to the tumor bed and unscheduled treatment breaks. This can have a detrimental effect on local tumor control and thus patient survival.[4]

Management of mucositis is critical to maintain the patients food pathway, avoid interruption in the delivery of radiation treatment and to avoid hospitalization and the need for parenteral or tube feeding. Currently there is no standard treatment for oral mucositis in head and neck cancer patients worldwide. Food and Drug Administration (FDA) have no approved intervention for prevention of radiation induced mucositis.[5] Current management of oral mucositis is limited to symptom control including pain relief and maintenance of good oral hygiene. One of the latest interventions for the management of radiation induced oral mucositis is natural honey.[6,7,8,9] It has antimicrobial properties[10] and promotes wound healing.

The main objective of this study is to know the effect of topical application of honey on onset and severity of radiation induced mucositis in head and neck cancer patients receiving radiation.

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How to cite this article: John Winkle Medida, Bala Sankar Ramavath, Joseph Benjamin Gandi. Effect of Honey in Radiation Induced Mucositis in Head and Neck Cancer. International Journal of Contemporary Medical Research 2016;3(1):108-113.

MATERIALS AND METHODS

Present study was done in the department of radiotherapy in MNJ Institute of Oncology & Regional Cancer Centre. The patients were randomly selected from year 2012 to 2014 and were allotted study group and control group.

Inclusion Criteria

Histo-pathologically confirmed non-metastatic Squamous cell carcinoma of head and neck region, age less than 70 years, ECOG performance status of 0-2, Patients should receive Concurrent Chemo radiotherapy as primary treatment.

Exclusion criteria

Tumors of non-Squamous histology, age greater than 70 years, ECOG performance status of >2, any prior treatment received for the tumor, any co-morbid condition or acute infection where treatment is contraindicated, evidence of distant Metastasis.

Patients Recruitment

56 patients receiving concurrent chemo radiotherapy to head and neck cancers were recruited in this study during October 2012 to august 2014. 27 were taken in study group and remaining 29 were taken into control group. Study group received 10ml of natural honey(Carom Plant) procured from NIRD(National Institute of Rural Development) for topical application in oral cavity 10min before and after radiation treatment. They were asked to swirl honey in oral cavity and swallow it slowly so that it can be smeared on oral and pharyngeal mucosa before and after every radiation fraction. Control group patients received only chemo radiotherapy. Both study group and control group patients were advised to take plenty of oral fluids, supplementation with high protein diet and oro-dental care.

Radiation Treatment Planning and Delivery

All patients underwent pre RT oro-dental care. Radiotherapy was delivered by linear accelerator (LINAC) using 6MV X rays. Computer based CT planning was done for all patients in two phases with total dose of 66Gy/33#.

PhaseI: 44Gy/22 fractions, 5 fractions per week

PhaseII: 22 Gy/11 fraction, 5 fraction per week, sparing the spinal cord.

Patients in both arms received concurrent chemotherapy with cisplatin 40 mg/ m2 given weekly with radiotherapy

Toxicity Assessment

All Patients were assessed twice a week (3#&5# in 1wk, 8# &10# in 2wk, 13# &15# in 3wk,18# &20# in 4wk, 22# in 5wk, 25# &28# in 6wk, 30# &33# in 7wk) for tumor response and development of mucositis. Mucositis was examined clinically under good light. RTOG (Radiation Therapy Oncology Group) grading system was utilized to grade the mucositis.

RTOG Grading System

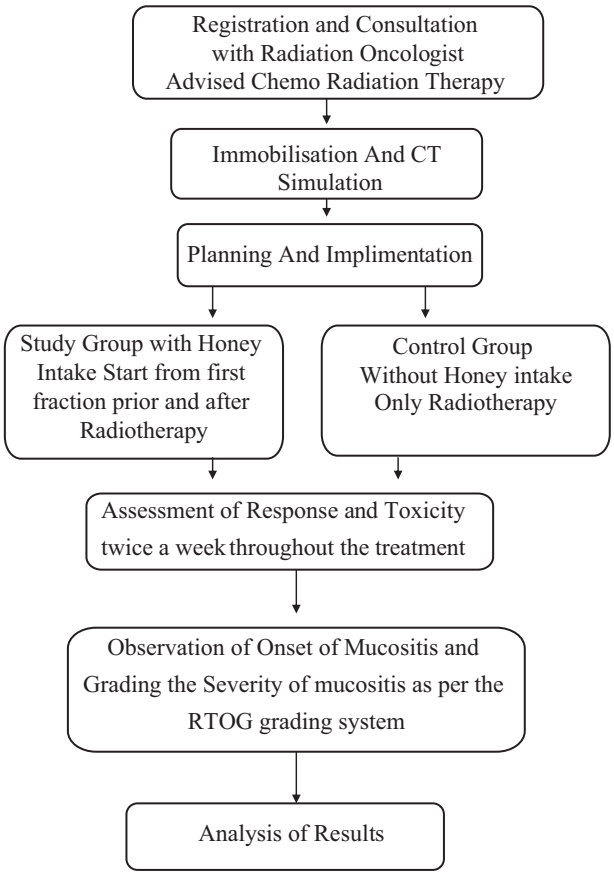
Grade 0 : No change
Grade 1 : Mucosal erythema
Grade 2 : Studded mucositis / Patchy mucositis
Grade 3 : Confluent mucositis not requiring intervention
Grade 4 : Ulceration necessitates for treatment break.

Data Collection and Statistical Analysis

The collected data was analyzed using standard statistical software package (SSPS
version 20.0). The onset and severity of mucositis were analyzed in both groups. The two groups were compared using chi square test to check whether they were balanced in terms of patient and disease related characters like stage, sex, tumor site, performance status, age, and histology.

RESULTS

Patients were selected according to inclusion and exclusion criteria. Total of 56 patients with Head and Neck cancers were enrolled. Study group consisted 27 patients and control group consisted 29 patients. Patients were in the age group of 25-58 years in study group whereas 30-62 in control group. The mean age of patients in study group was 40.6 The mean age of patients in control group was 48.03.The patients were assessed regularly twice a week for the onset of mucositis and severity of mucositis according to RTOG mucositis grading system.



Fraction	study	control	Total	Df	X^2
Eight	1(3.7%)	12(41.4%)	13(23.2%)	4	0.000
Ten	10(37%)	15(51.7%)	25(44.6%)		
Thirteen	15(55.6%)	2(6.9%)	17(30.4%)		
Fifteen	1(3.7%)	0(0%)	1(1.8%)		

Table-1: Onset of mucositis in study group and control group

Fractions	Grade	Study	Control	DF	X^2
3#	G0	27 (48.2%)	29 (51.8%)	NS	NS
w5#	G0	27 (48.2%)	29 (51.8%)	NS	NS
8#	G0 G1 G2	26 (96.3%) 1(3.7%) 0 (0%)	17 (58.6%) 11(37.9%) 1(3.6%)	2	0.004
10#	G0 G1 G2	16 (59.3%) 8(29.6%) 3(11.1%)	2 (6.9%) 13(44.8%) 14(48.3%)	3	0.000
13#	G0 G1 G2	1 (3.7%) 21(77.8%) 5(18.5%)	0(0%) 5(17.2%) 24(82.8%)	2	0.000
15#	G1 G2 G3	15(55.6%) 12(44.4%) 0(0%)	0(0%) 25(86.2%) 0(0%)	2	0.000
18#	G1 G2 G3	6(22.2%) 19(70.4%) 2(7.4%)	0(0%) 14(48.3%) 15(51.7%)	2	0.000
20#	G1 G2 G3	21(77.8%) 6(22.2%) 0(0%)	4(13.8%) 24(82.8%) 1(3.4%)	2	0.000
22#	G2 G3 G4	15(57.7%) 11(42.3%) 0(0%)	1(3.4%) 21(72.4%) 7(24.1%)	2	0.000
25#	G1 G2 G3 Absconded	8(28%) 16(64%) 1(4%) 1(4%)	0(0%) 24(82.8%) 3(10.3%) 2(6.9%)	3	0.006
28#	G1 G2 G3	12(50%) 12(50%) 0(0%)	1(3.7%) 23(85.2%) 2(7.4%)	3	0.001
30#	G0 G1 G2 G3	3(12.5%) 13(54.2%) 8(33.3%) 0(0%)	0(0%) 4(15.4%) 21(80.8%) 1(3.8%)	3	0.002
33#	G0 G1 G2 G3	5(20.8%) 14(58.3%) 5(20.8%) 0(0%)	0(0%0 5(19.2%) 20(76.9%) 1(3.8%)	3	0.000

Table-2: Assessment of mucositis at every fraction in study group and control group

Onset of Mucositis

The onset of mucositis in study group and control group was as follows:

1 (3.7%) patient in study group and 12(41.4%) patients in control group developed grade1 mucositis at 8th fraction. 10 (37%) patients in study group and 15(51.7%) patients in control group developed grade 1 mucositis at 10th fraction. 15 (55.6%) patients in study group and 2(6.9%) in control group developed mucositis at 13th fraction.

The mucositis was assessed twice a week. The following table shows the grades of mucositis on every assessment.

None of the patients in study group and control groups developed mucositis at 3#.

DISCUSSION

Radiation-induced mucositis is a normal accompaniment of radiotherapy to the head and neck area. Normally, the oral mucosa has a relatively high cell-turnover rate. Exposure to ionizing radiation leads to mucosal erythema, small whitish patches and ultimately results in confluent mucositis.[11] In later phases, oral ulceration and bleeding become a dose-lim-

Study Group		Control Group	
Fraction	**Mean muco-sitis score**	**Fraction**	**Mean muco-sitis score**
Eight	0	Eight	0.44
Ten	0.4	Ten	1.41
thirteen	1.1	thirteen	1.82
Fifteen	1.4	Fifteen	2.13
Eighteen	1.8	Eighteen	2.51
Twenty	2.2	Twenty	2.89
Twenty two	2.4	Twenty two	3.2
Twenty five	1.7	Twenty five	2.11
Twenty eight	1.3	Twenty eight	2.03
Thirty	1.1	Thirty	1.88
Thirty three	0.9	Thirty three	1.84

Table-3: Mean muositis score for study group and control group

iting toxicity. Mucositis a result of imbalance between cell loss and cell proliferation. The intensity of mucositis can be altered by new fractionation schedules, concurrent chemo-radiotherapy and co-morbid medical conditions. Bacterial colonization in the oral mucosa can aggravate the pre-existing mucositis.[12] Endo toxins released from the gram-negative bacilli are potent mediators of the inflammatory process in the oral mucosa. Oropharyngeal flora, too, contributes to the radiation-induced mucositis.

The basis of management of radiation mucositis is targeted to its four defined

Pathogeneses[13]:

- To check basal cell layer growth by modifying transforming growth factor β3.
- Stimulation of epithelization, thereby encouraging rapid recovery of cell loss.
- chemical protection of mucosa using the Amino-Thiol group of compounds like amifostine.
- Physical protection of oral mucosa by shield use, Conformal therapy or Intensity modulated radiotherapy.

There is no standard treatment for radiation induced mucositis. In this study, honey is used topically over mucosa prior to and after radiation treatment every day during the entire course of treatment starting from first fraction, to know the effectiveness on radiation induced mucositis. Honey is naturally available, cheap, and ubiquitous and exhibits antibacterial, analgesic and tissue nutritive factors to stimulate re epithelization in damaged mucosa.[14,15,16,17,18]

Age and Sex of patients

According to (Dodd,1999), younger patients of age less than 20 years are more susceptible for oral mucositis due to more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors in the epithelium at the early age.[19,20] On the other hand, the physiologic decline in renal function associated with aging may result in higher incidence of oral mucositis in older patients.[19]

Onset of Radiation Induced Mucositis

No patients developed RIM at 5th fraction assessment either in study group or control group. The onset of mucositis in control group patients at 8th (41.4%) &10th (51.7%) constituted 93.1% of control group patients whereas the onset of mucosis at 10th (37%) & 13th (55.6%) in study group patients constituted 92.6% of patients of study group.

Biswal et al. (2003) conducted a clinical trial investigating the effect of tea plant honey on oral mucositis in patients receiving radiation therapy. In their study, 40 patients with oropharyngeal carcinoma were divided into two groups to receive radiation alone or radiation plus topical application of pure natural honey. They reported a significant reduction in the severity of oral mucositis in those patients treated with honey. Only 25% of patients in the honey group developed grade three or four mucositis compared to 75% in the control group.

Sadakshetram jayachandran et.al, 2012, conducted a study to evaluate the effect of natural honey and 0.15% benzydamine hydrochloride on the onset and severity of radiation induced mucositis. They assessed patients daily, for the onset and severity of mucositis. The onset of mucositis for honey group was on 14th day compared to 12th day for 0.15% benzydamine and control group.

The present study results also showed the onset of mucositis for majority of study group patients was at 13th fraction whereas for control group patients was at 10th fraction inferring honey postpones the onset of mucositis.

SEVERITY OF MUCOSITIS

The current study assessed mucositis twice a week till the end of radiation treatment. Thus patients were assessed at 3rd, 5th, 8th, 10th, 13th, 15th, 18th, 20th, 22nd, 25th,28th,30th and 33rd fractions.

Pattern of mucositis

All patients developed mucositis during radiation treatment. The severity of mucositis was increased as the fractions were increased and towards the end of the treatment severity was decreased in both groups.

The majority patients in study group developed mucositis around 10th & 13th fraction (92.6%) and majority of patients in control group developed around 8th & 10th fraction (93.4%). The severity of mucositis assessed at every fraction showed a statistically significant difference between study and control groups with p value of <0.01.

The results of this study were consistent with the following randomized controlled clinical trials investigating the effect of honey on oral mucositis, using a similar study protocol.

Motallebnejad et al. (2008) and Rashad et al. (2008) conducted similar trials using honey in Iran and Egypt respectively. Motallebnejad et al. (2008) evaluated 40 patients with 20 in each arm to receive and not to receive honey. Mucositis

was assessed with oral mucositis assessment scale(OMAS). The results showed significant reduction in mucositis among honey received patients compared with controls with p value of 0.000. Rashad et al. (2008) randomized 40 patients to study group to receive honey topically along with radiotherapy and control group only with radiotherapy. Patients were assessed weekly for the development of mucositis. No patients in the study group developed grade 4 mucositis and only 15% of patients developed grade 3 mucositis whereas 65% of patients developed grade3/4 mucositis in control group ($p<0.05$). Motallebnejad et al. (2008) used saline mouthwashes and Rashad et al. (2008) used Benzydamine HCl mouthwashes for all patients.

Sadaksharam jayachandran et al. evaluated 60 patients and divided them into 20patients each group taking honey orally,0.15% benzydamine chloride and normal saline during radiation treatment. They found pure natural honey delays the onset of radiation induced mucositis and significantly reduce the severity of mucositis. The differences between the groups were statistically significant ($P < 0.001$).

Important factors that influence the effectiveness of honey:

Its hygroscopic nature, acidic pH prevents bacteria growth when applied to the mucosa, Inhibin (hydrogen peroxide) converted from glucose oxydase and gluconic acid, Enzymes (growth factors?) and tissue-nutritive minerals and vitamins help repair tissue directly.

The antibacterial property of honey depends upon its concentration. The effect on radiation mucositis in honey treated patients might be due to the bacteriostatic effect of viscid honey. Pure honey is acidic, with a pH of around 3.9. The solubility reducing factor present in honey can activate in absence of saliva. Honey applied on radiation induced xerotic mucosa increases the micro hardness of enamel, thereby preventing caries. Hence, it has been postulated that honey is less Cariogenic in dry mouth patients.

There are currently no approved agents or strategies that reliably prevent RIM, although several agents are under investigation. The current recommendations for mucositis are directed at limiting its extent and/or severity by appropriate treatment selection, attention to RT planning details, and the use of supportive and palliative care including basic oral care, aggressive use of analgesics, the use of feeding tubes in selected cases, and swallowing exercises and therapy. Honey has been found effective in burn wounds, oral infections and acceleration of surgical wound healing. Pure honey is ubiquitous, cheap and natural, and exhibits antibacterial, analgesic and tissue nutritive factors to stimulate re epithelization in the damaged mucosa, and is thereby a justified agent to try in radiation mucositis. Through this study, topical application of honey can be used as an effective intervention to prevent the radiation induced mucositis.

CONCLUSION

1. This small prospective interventional study found the usefulness of topical application of honey in reducing the onset as well as severity of radiation induced mucositis in patients receiving radiation to head and neck cancers.
2. The results of the study are similar with three overseas studies Biswall et al., 2003; Motallebnjad et al., 2008 and Rashad et al., 2008 and one Indian study by Sadaksharam jayachandran and Narasimhan Balaji,2010.

Limitations

1. The sample of patients is small.
2. The study group is not representative of entire head and neck cancer patients.
3. Non randomization of patients.

Recommendations

This study evaluated patients for radiation induced mucositis twice a week. By this, the exact fraction/dose of development of mucositis can not be assessed properly. Instead if assessed daily, the exact fraction/dose at which the mucositis starts can be known. The effect of honey on the radiation dosimetry should be studied, if it is adopted as one of the modality of treatment of radiation induced mucositis.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 21-11-2015; **Published online**: 05-12-2015