ROLE OF HONEY IN PREVENTION OF RADIATION INDUCED MUCOSITIS IN HEAD AND NECK CANCER

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ABSTRACT

Objective: To determine the efficacy of honey in preventing radiation induced mucositis (RIM) in patients with head and neck cancers.

Design: Randomized controlled trial.

Setting: Oncology Department of Combined Military Hospital Rawalpindi, from July 2011 to September 2012.

Patients and Methods: Sixty patients diagnosed with head and neck cancer requiring radiotherapy to the oropharyngeal mucosa were randomized into two groups to receive either radiation alone or radiation and natural honey. Patients were treated using 6-MV X-ray beams from linear accelerator at a dose rate of 2 Gy per day five times a week up to a dose of 66 Gy. In the treatment group, patients were advised to take 20 ml of pure honey 15 minutes before, 15 minutes after and 6 hours after radiotherapy. Patients were evaluated every week for the development of RIM using the WHO oral mucositis grading system.

Results: In treatment group, out of 30 patients, 4(13%) developed grade 3 RIM and none developed grade 4 RIM. In control group, out of 30 patients, 12 (40%) developed grade 3 or 4 RIM (p=0.039). Four patients (13%) in treatment group lost more than 5 Kg weight during the course of radiotherapy compared to 16 patients (53%) in control group (p=0.002).

Conclusion: The results of our study have shown that honey is a simple and cost effective treatment to prevent RIM. Large scale randomized trials are needed to confirm the results of our study.

Keywords: Honey, Radiation induced mucositis.

INTRODUCTION

Radiation-induced mucositis (RIM) is experienced in about 80% patients with head and neck cancers undergoing radiation therapy[1]. RIM is typically associated with pain, discomfort, dysphagia, dehydration, micronutrient deficiency, weight loss and potentially life threatening aspiration. It may disrupt the function and integrity of the mucosa resulting in patient's inability to eat and swallow, interference with the radiotherapy schedule, and increase in the likelihood of hospitalization[1,2]. The extent of the injury is directly related to the mucosal volume irradiated, anatomic subsite exposed, treatment intensity, and individual patient's predisposition[3].

Unfortunately, to date, there is no standard effective treatment to prevent radiation induced mucositis. Many agents have been tried, with various response rates, including subcutaneous or topical granulocyte macrophage colony stimulating factor, the prostaglandin-E analogue Misoprostol, topical corticosteroids, allopurinol, aloe vera, cryotherapy, intravenous glutamine, polymixin / tobramycin/ amphotericin (PTA) antibiotic paste and the parenteral radio-protector amifostine[3]. Strategies to limit the extent of mucositis and to manage its symptoms include basic oral care and supportive medications.

Honey is a by-product of flower nectar and the upper aero-digestive tract secretions of the honeybee, which is concentrated through a dehydration process inside the bee hive[4]. Because of its high viscosity, acidic pH, hydrogen peroxide, high osmolarity, and rich nutritional properties honey can inhibit bacterial growth and enhance healing[5-7]. This study evaluated the effectiveness of honey in preventing RIM

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compared with normal saline in patients with head and neck cancers undergoing radiotherapy.

PATIENTS AND METHODS

This randomized controlled trial was conducted between July 2011 to September 2012 at department of Oncology, Combined Military Hospital (CMH), Rawalpindi, Pakistan. The following criteria were used to enroll patients in the study.

Inclusion criteria:

- Patients with histologically confirmed, non-metastatic carcinoma of the head and neck.
- Patients with age ≥ 20 and ≤ 70 years.
- Patients with Eastern Cooperative Oncology Group performance status 2 or less.
- Patients requiring radical radiotherapy which included a significant area (more than 50%) of directly visible oral and/or oropharyngeal mucosa in the radiation field (55 to 66 Grays).

Exclusion criteria:

- Patients with more than one malignancy.
- Patients who have received previous radiotherapy to head and neck region.
- Patients with abnormal liver or renal function.
- Patients with abnormal haematological profile.
- Patients with early glottic cancer (T1 and T2).
- Patients with co-morbid medical conditions such as diabetes mellitus or connective vascular disorders.
- Patients with poor oro-dental hygiene.
- Patients who continue to smoke or use oral tobacco products like snuff dipping.

With the approval from the Hospital Ethical Committee, sixty patients from Oncology out patient department (OPD) at CMH, Rawalpindi were enrolled in the trial after obtaining their informed written consent. Patients were randomized by using table of random numbers. The patients in the control group were matched to the study group by sex, age, the site of the primary tumor, radiation dose, concurrent and sequential chemotherapy, and general health status. Patients were treated using a 6-MV linear accelerator at a dose rate of 2 Gy per day five times a week up to a dose of 66 Gy. The study group of thirty patients took 20 ml pure natural honey 15 minutes before and at 15 minutes and 6 hours after radiotherapy. They were instructed to rinse the honey around in their mouths and swallow gradually in order to coat the oral and pharyngeal mucosa. The thirty patients in the control group were advised to rinse their mouth with 20 ml of normal saline before and after each radiotherapy session. Mucositis grade using the World Health Organization (WHO) grading system (Table 1) and patients weight were recorded at baseline (Day 0) before intervention and weekly during treatment and 15 days after completion of treatment.

Data analysis was done with the help of the Statistical Package for the Social Sciences (SPSS) version 19 software, which included descriptive analysis and chi-square comparison. p value of <0.05 was considered statistically significant.

RESULTS

The demographic characteristics of patients in treatment group (n=30) and control group (n=30) were well balanced. Table 2 shows patients characteristics regarding sex, age and site of primary tumor. Out of thirty patients in treatment group, 4 (13%) developed grade 3 mucositis and none developed grade 4 mucositis. In control group, out of thirty patients, three (10%) developed grade 4 mucositis and nine (30%) developed grade 3 mucositis (p=0.039) (Figure 1). Radiation therapy was interrupted in three control group patients (10%) because of severe mucositis compared to none in treatment group. The median discontinuation period was 10 days (range 7 to 13 days). Sixteen patients (53%) in control group lost more than 5 Kg weight during the course of radiotherapy

compared to only four patients in control group (p=0.002).

DISCUSSION

Honey is an ancient nutraceutical that may exhibit anti-inflammatory and antibacterial propertie[8]. Bergman et al showed that un-boiled honey, when applied topically induces rapid epithelialization of tissue injuries. They postulated that the effect may be the result of honey's energy-producing properties, its hygroscopic effect on the wound and its bacteriostatic properties[9]. Antiseptic properties of honey are mainly due to its acidic pH, high osmolarity and hydrogen peroxide contents[10]. We used raw natural honey obtained from bee hives in northern Pakistan, an area of biodiversity.

Biswall et al used topical honey to manage RIM successfully for the first time[4]. They demonstrated a significant reduction (20% vs 75%) in grade 3 and 4 RIM by using honey. The study was replicated by Motallebnejad et al[11] and Rashad et al[12], who reported similar findings. In the study by Rashad et al there was a significant reduction in grade 3 and 4 RIM among honey treated patients compared to control group i.e 15% versus 65% ($p < 0.05$)[12]. In a study by Khanal et al the proportion of patients with intolerable oral mucositis was lower in the honey group and this was statistically significant ($p = 0.000$)[13]. In all of these studies 20 ml of pure natural honey is used three times a day and we followed the same dosage. A systemic review and meta-analysis demonstrated an overall relative risk reduction of 80% in the honey treatment group compared with the control based on the above mentioned studies[14]. Our results are similar to these studies. We not only found a statistically significant reduction in the onset and severity of RIM in patients treated with honey but also these patients lost less weight compared to patients not receiving honey. Further-more patients receiving honey had no unwanted breaks in treatment delivery, had less hospital stay and recovered quickly from acute radiation toxicity. Pleasant taste of honey was well accepted by the patients.

In a study by Bardy et al there was no

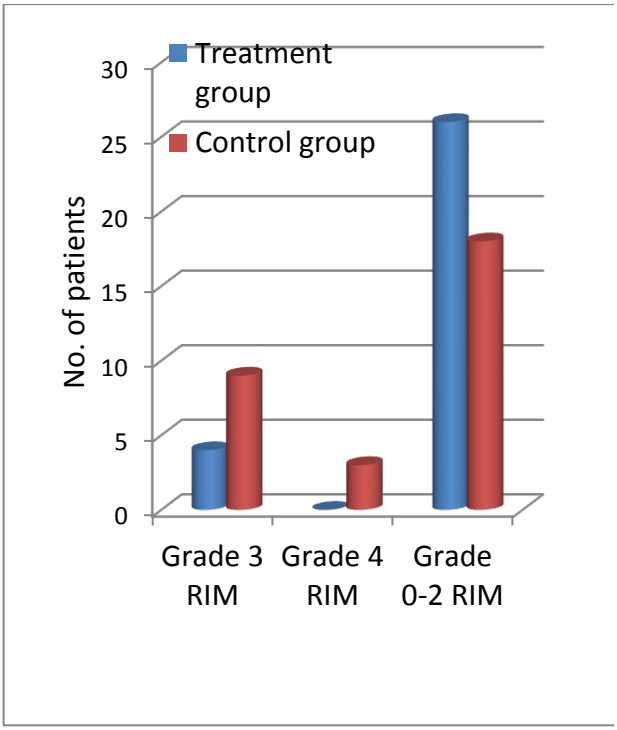

Figure-1: Comparison of radiation-induced mucositis (RIM) in treatment and control group.

Table-1: World Health Organization (WHO) oral mucositis grading.

Grade	Pathology
0 (none)	None
1 (mild)	Oral soreness, erythema
2 (moderate)	Oral erythema, ulcers, can eat solids
3 (severe)	Oral ulcers, requires liquid diet only
4 (life threatening)	Oral alimentation not possible

significant difference between manuka honey and golden syrup in their effects on RIM[15]. They found that active manuka honey did not improve mucositis, but both the honey and the syrup seemed to be associated with a reduction in bacterial infections. Our study results are contradictory to the results of study by Bardy et

al. Although we did not carry out oral mucosal bacterial cultures in both groups but our results did show statistically significant reduction in incidence of severe RIM in patients treated with topical honey.

Table-2: Comparison of demographic characteristics of patients in treatment and control group.

Parameter	Treatment group (n = 30)		Control group (n = 30)		*p*-value
	n	%	n	%	
Sex					
Male	19	63	20	67	0.787
Female	11	37	10	33	
Age					
20-30 years	02	07	02	07	
31-40 years	05	17	04	13	
41-50 years	11	37	12	40	0.986
51-60 years	08	26	09	30	
61-70 years	04	13	03	10	
Tumor site					
Oral cavity	18	60	18	60	0.920
Hypopharynx	07	23	06	20	
Nasopharynx	05	17	06	20	

Different studies carried so far have used different grading systems to assess the severity of RIM. We preferred WHO radiation therapy oncology group oral mucositis grading system, previously used by Rashad et al[12] because it incorporates both objective physical findings and subjective patients input. Compared to Oral Mucositis Assessing Scale (OMAS), used by Motallebnejad et al[11], it is easy to use and is reproducible.

Normal saline was used in control group because there is no ideal placebo available. The study was not blinded. Another limitation was the quality control of honey. Since enzymes and chemicals found in honey are heat sensitive[16], we used raw natural honey instead of edible honey retailed in markets which is often processed. Honey quality also depends upon source and dilution[17].

The effects of different doses of honey on RIM is not well studied. Increasing dose of honey may help in combating nutritional deficiencies owing to high caloric value of honey. Whether reducing the dose of honey is equally effective in preventing onset and severity of RIM is not known. In future, well designed trials may answer these questions.

CONCLUSION

With its limitation, the results of our study have shown that honey is a simple, cost effective, readily available and well accepted treatment in preventing RIM. Further large scale studies are required to validate the results of our study and to find optimal dosage schedule for honey in preventing RIM.

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