# Honey as topical prophylaxis against radiochemotherapy-induced mucositis in head and neck cancer

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#### Abstract

Aim: To evaluate the efficacy of pure natural honey as prophylaxis against radiochemotherapy-induced mucositis, through clinical scoring of oral and oropharyngeal mucositis, and culturing of pathogenic oral and oropharyngeal microbes.

Patients and methods: The study was done in Assiut University Hospital, Egypt, between January 2005 and July 2006. Forty patients diagnosed with head and neck cancer were entered into the trial. Enrolled patients were randomised to either the treatment group, receiving concomitant chemotherapy and radiotherapy (with a significant area of directly visible oral and/or oropharyngeal mucosa included in the radiation fields) plus prior topical application of pure natural honey, or the control group, receiving concomitant chemotherapy and radiotherapy without honey. Patients were evaluated clinically every week to assess development of radiation mucositis. Aerobic cultures and candida colonisation assessment were undertaken, via oral and oropharyngeal swabs, prior to and at the completion of irradiation, and when infection was evident.

Results: In the treatment group, no patients developed grade four mucositis and only three patients (15 per cent) developed grade three mucositis. In the control group, 13 patients (65 per cent) developed grade three or four mucositis (p < 0.05). Candida colonisation was found in 15 per cent of the treatment group and 60 per cent of the control group, either during or after radiotherapy (p = 0.003). Positive cultures for aerobic pathogenic bacteria were observed in 15 per cent of the treatment group and 65 per cent of the control group, during or after radiotherapy (p = 0.007).

Conclusion: This study shows that prophylactic use of pure natural honey was effective in reducing mucositis resulting from radiochemotherapy in patients with head and neck cancer.

#### Key words: Head and Neck Neoplasms; Radiotherapy; Honey; Mucositis

#### Introduction

All patients receiving concomitant chemotherapy and radiotherapy in the head and neck region develop oral mucositis.<sup>1</sup> Mucositis is a result of imbalance between cell loss and cell proliferation. Bacterial colonisation of the oral mucosa can aggravate pre-existing mucositis. Endotoxins released from Gram-negative bacilli are potent mediators of the inflammatory process in the oral mucosa.<sup>2,3</sup> Mucositis may lead to suboptimum effectiveness of chemotherapy and radiotherapy.<sup>4</sup> Effective management of this complication is therefore very important. There is currently no known intervention which is completely successful in preventing or treating oral mucositis.<sup>5</sup> Many agents have been tried, with various response rates, including: subcutaneous or topical granulocyte macrophage colony stimulating factor,<sup>6</sup> the prostaglandin-E analogue misoprostol,<sup>7</sup> topical corticosteroids<sup>8</sup> and the parenteral radio-protector amifostine.<sup>9</sup>

The Qur'an vividly illustrates the potential therapeutic value of honey.

Thy Lord has inspired the Bees, to build their hives in hills, on trees and in man's habitations, From within their bodies comes a drink of varying colours, wherein is healing for mankind, Verily in this is a Sign, for those who give thought.<sup>10</sup>

Biswal *et al.*<sup>11</sup> reported that topical application of natural honey is a simple and cost-effective treatment for radiation mucositis, and recommended further, multi-centre, randomised trials to validate their findings.

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Honey has been used medically throughout history. In more recent times, it has been rediscovered by the medical profession for the treatment of burns, infected wounds and skin ulcers.<sup>12</sup> The rationale of using honey to manage radiation mucositis was derived from basic research and clinical observation of rapid epithelialisation in tissue injuries.<sup>13</sup> Bergman et al. reported that unboiled honey seemed to result in accelerated wound healing when applied topically, and theorised that this effect might be due to its energy-producing properties, its hygroscopic effect on the wound and its bacproperties. How much teriostatic of this bacteriostasis is due to honey's inherent antimicro-bial properties<sup>14</sup> and how much to its hyperosmolar nature is unknown. Pure honey is acidic, with a pH of around 3.9. A solubility-reducing factor present in honey can activate in the absence of saliva. Honey applied to radiation-induced xerotic mucosa increased the micro-hardness of enamel, thereby preventing caries. Hence, it has been postulated that honey is less cariogenic in patients suffering dry mouth.<sup>15</sup>

In this study, we used honey derived mainly from the clover plant *Trifolium alexandrenum*.

The large volume of literature reporting the effectiveness of honey indicates that it may potentially be useful to treat periodontal disease, mouth ulcers and other problems of oral health.<sup>12</sup>

#### **Patients and methods**

This study was conducted between April 2005 and July 2006 in Assiut University Hospital, Faculty of Medicine Assiut University departments of Ear, Nose and Throat; Oncology and clinical pathology; where the study patients were assessed and treated; and Faculty of Agricalture, Assiut branch, Al-Azhar University, Egypt. It included 40 patients diagnosed with head and neck cancer who satisfied the following criteria.

#### Inclusion criteria

Patients included in the study satisfied the following criteria: histologically confirmed, nonmetastatic carcinoma of the oral cavity, pharynx (nasopharynx, oropharynx or hypopharynx) or larynx; patients with tumour-node-metastasis (TNM) stagings of  $T_X, T_1-T_4, N_X, N_0-N_3$  and  $M_0$ ; Karnofsky performance status<sup>16</sup> of  $\geq$ 50 per cent; those requiring radical radiotherapy which included a significant area of directly visible oral and/or oropharyngeal mucosa in the radiation field (a significant area was defined as two or more anatomical sites at risk, e.g. the soft palate and the cheeks, or the floor of the mouth and the tongue);<sup>17</sup> and normal renal and hepatic function and normal haematological values (i.e. white blood cells >3.0  $\times$  10<sup>9</sup>/l, platelets >100  $\times$  10<sup>9</sup>/l and haemoglobin >10 g/dl).

#### Exclusion criteria

Patients were excluded if they met the following criteria: early glottic cancer ( $T_1$  and  $T_2$ ); previous chemotherapy or radiation treatment to the upper airways; previous radical surgery of the primary tumour and/or regional lymph nodes; and co-morbid medical conditions such as diabetes mellitus or connective vascular disorders.

#### Study design

Enrolled patients were randomised to either the treatment group, to receive concomitant chemotherapy and radiotherapy plus topical application of pure natural honey, or the control group, to receive concomitant chemotherapy and radiotherapy without honey.

*Pretreatment evaluation.* This consisted of a complete history, physical examination including flexible fibre-optic endoscopy, complete blood analysis, liver function tests, chest X-ray, and computed tomography or magnetic resonance scans of the head and neck to assess the extent of the primary tumour as well as the neck nodes. Patients also underwent panendoscopy of the upper aerodigestive tract and biopsy for histopathological examination. All patients received pretreatment dietary counselling and dental evaluation.

Radiotherapy. This was delivered using a 6-MV linear accelerator or Cobalt-60 at a dose fraction of 2 Gy per day five times a week, without any intended gaps, up to a dose of 60-66 Gy (depending on TNM classification;  $T_1$  and  $T_2$  tumours and negative nodes were treated with a dose of 60 Gy, while patients with  $T_3$ ,  $T_4$  and/or positive nodes were treated with a dose of 66 Gy). Reproducibility of head and neck positioning was achieved by using a fixation device (Orfit mask; MEDTEC Inc Orange City, Iowa, USA). The treatment volume included the primary tumour site plus adequate margins and the neck nodes at risk. Usually, parallel-opposed fields were used to irradiate the primary tumour and the upper neck. A separate, anterior supraclavicular field was used to irradiate the lower neck and supraclavicular fossa. The spinal cord was protected after 40 Gy. The prescribed dose was 50 Gy to the clinically negative neck and 60-66 Gy to the gross target volume and positive neck nodes.

*Chemotherapy.* This consisted of cisplatin ( $20 \text{ mg/m}^2$  infusion once a week before radiotherapy). All patients received adequate hydration and a serotonin antagonist to prevent vomiting during cisplatin administration. Full blood count examination was performed weekly. If the white blood cell count was lower than  $3.0 \times 10^9$ /l, the platelet count below  $100 \times 10^9$ /l, or haemoglobin less than 10 g/dl, the subsequent chemotherapy dose was delayed for one week, without interruption of radiotherapy.

HONEY FOR RADIOCHEMOTHERAPY-INDUCED MUCOSITIS

TABLE I

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

WHO = World Health Organization

Honey. In the treatment group, patients were advised to smear the inside their mouth with 20 ml of pure honey, 15 minutes before, 15 minutes after and 6 hours after radiation therapy (as per Biswal and colleagues' protocol).<sup>11</sup> They were advised to rinse honey on the oral mucosa and then to swallow it slowly, in order to smear it onto the oral and pharyngeal mucosa. The above treatment was advised throughout the course of radiotherapy.

Quality control of honey. The main flower involved in the collection of nectar was that of the clover plant Trifolium alexandrenum. Honey so produced was filtered and supplied as raw (i.e. pure) honey for the trial. The honey was subjected to analysis of chemical composition, pH, density and viscosity. Thin layer chromatography was used for the chemical analysis. The honey was extracted with potassium ether, chloroform, ethyl alcohol and methyl alcohol and developed to meet a MeOH:H<sub>2</sub>O:CHCl<sub>3</sub> ratio of 50:10:64. Chemical analysis indicated that the honey had a pH of 4.1 and contained such compounds as terpenoids, trace elements, nitrogenous compounds and sugars. Viscosity was 3.8 N and density 1.4 g/ml.

Toxicity criteria. Patients were evaluated clinically every week in order to detect the development of radiation mucositis, using the World Health Organization (WHO) Radiation Therapy Oncology Group grading system (Table I).<sup>18</sup>

Treatment delays or gaps were recorded for cases of intolerable mucositis; the total number of treatment days lost was also recorded.

Microbiological cultures. In order to study the antimicrobial effect of honey on patients' oral mucosa, aerobic cultures and candida colonisation tests were performed. Oral and oropharyngeal swabs were taken from areas to be irradiated, prior to and at the completion of irradiation, and also when infection was evident.

Oral care. During the study, patients were instructed to use benzydamine HCl (EPICO, Cairo, Egypt), a nonsteroidal analgesic and anti-inflammatory compound, plus supportive oral care measures. Dental evaluation was undertaken before and after radiotherapy. Antibiotics and antifungals were only used if indicated by clinical examination and culture and sensitivity results. All patients were given pretreatment dietary counselling, reinforced weekly. A nasogastric feeding tube was placed when and if needed (i.e. for grade four mucositis with absolute dysphagia).

#### Statistical analysis

Data were entered into a Microsoft Excel 2003 spreadsheet. The Statistical Package for the Social Sciences version 13 software was used for data analysis, which included descriptive analysis and Yates

PATIENT CHARACTERISTICS									
Parameter	Treatment group		Control group		Total				
	n	%	n	%	n	%			
Sex									
Male	16	80	15	75	31	77.5			
Female	4	20	5	25	9	22.5			
TNM stage									
T <sub>1</sub>	0	0	0	0	0	0			
$T_2$	5	25	6	30	11	27.5			
$\overline{T_3}$	7	35	5	25	12	30			
$T_4$	8	40	9	45	17	42.5			
N <sub>0</sub>	8	40	9	45	17	42.5			
N <sub>1</sub>	3	15	6	30	9	22.5			
$N_2$	6	30	5	25	11	27.5			
N <sub>3</sub>	3	15	0	0	3	7.5			
Tumour site									
Oral cavity	3	15	2	10	5	12.5			
Nasopharynx	1	5	2	10	3	7.5			
Oropharynx	2	10	1	5	3	7.5			
Hypopharynx	6	30	7	35	13	32.5			
Larynx	8	40	8	40	16	40			
RT target dose (cGy)									
6000	5	25	4	20	9	22.5			
6600	15	75	16	80	31	77.5			
Age (years)									
Mean	47.65		48.18		48.20				
SD	13.17204		10.459		15.63723				

TABLE II

TNM = tumour-node-metastasis; RT = radiotherapy; SD = standard deviation

corrected chi-square analysis. Graphs were produced using Microsoft Excel 2003.

### Results

## Patients

The characteristics of the patients and their tumours were comparable for the treatment group (n = 20)and the control group (n = 20) (Table II). Primary tumours were located in the oral cavity (five), nasopharynx (three), oropharynx (three), hypopharynx (13) and larynx (16). Radiotherapy treatments were similar in the treatment and control groups. In all patients, chemotherapy was administered concurrently with radiotherapy, as previously described. All treatment group patients received honey throughout their radiotherapy course. Table II shows patients' characteristics regarding sex, TNM staging and tumour site.

In the treatment group, no patients developed grade four mucositis and only three (15 per cent) developed grade three mucositis. However, in the control group, three patients (15 per cent) developed grade four mucositis and nine patients (45 percent) developed grade three mucositis.



FIG. 1 Occurrence of various grades (G) of mucositis in (a) control group and (b) treatment group.

#### HONEY FOR RADIOCHEMOTHERAPY-INDUCED MUCOSITIS

The difference in the mucositis patterns is illustrated in Figure 1. There was a significant reduction in grade three and four mucositis in the treatment group. Five control group patients' (25 per cent) therapy was interrupted as a consequence of radiation mucositis, compared with none in the treatment group. The median discontinuation time was seven days (range, four to 10 days). These patients required nasogastric tube feeding, and both enteral and parenteral fluid and nutritional supplementation. Table III shows patients' distribution of mucositis during radiotherapy.

Candida colonisation was found in 20 per cent of the treatment group and 25 per cent of the control group before radiotherapy, and in 15 per cent of the treatment group and 60 per cent of the control group during or after radiotherapy. The difference between the two groups at the end of radiotherapy was statistically significant (p = 0.003).

Before radiotherapy, four of the 20 treatment group patients (20 per cent) and five of the 20 control group patients (25 per cent) had positive cultures for aerobic pathogenic bacteria. During or after their radiotherapy, three of the 20 treatment group patients (15 per cent) and 13 of the 20 control group patients (65 per cent) had positive cultures for aerobic pathogenic bacteria. The difference between the two groups was statistically significant (p = 0.007).

Occasionally, more than one type of bacteria were isolated from the same patient. However, in both treatment and control groups, the bacterial species most frequently isolated was *Staphylococcus aureus*, in 11 patients. Pneumococcus type species were detected in six patients, and pseudomonas in four patients.

#### Discussion

The rationale of using honey in managing radiation mucositis was derived from basic research and clinical observation of rapid epithelialisation of tissue injuries.<sup>13</sup> Bergman *et al.* reported that unboiled honey appeared to accelerate wound healing when applied topically; these authors theorised that the

effect may be due to honey's energy-producing properties, its hygroscopic effect on the wound and its bacteriostatic properties.<sup>13</sup> How much of this bacteriostasis is due to honey's inherent antimicrobial properties<sup>14</sup> and how much to its hyperosmolar nature is unknown. Pure honey is acidic, with a pH of around 3.9. A solubility-reducing factor present in honey can activate in the absence of saliva. Honey applied to radiation-induced xerotic mucosa increases the micro-hardness of enamel, thereby preventing caries. Hence, it has been postulated that honey is less cariogenic in patients suffering dry mouth.<sup>15</sup>

In this study, we used honey derived mainly from the clover plant *Trifolium alexandrenum*. We aimed to evaluate the efficacy of pure natural honey in managing chemoradiation-induced mucositis, through clinical scoring of oral mucositis and culturing of pathogenic oral microbes.

- Previous reports suggest that topical application of natural honey may provide simple and cost-effective prophylaxis against radiation mucositis
- This study showed that prophylactic use of pure natural honey was effective in reducing mucositis resulting from radiochemotherapy in patients with head and neck cancer
- The large volume of literature reporting the effectiveness of honey indicates that it may potentially be useful to treat periodontal disease, mouth ulcers and other problems of oral health

The results of this study show that honey can markedly reduce the incidence of radiochemotherapy-induced oral and oropharyngeal mucositis of WHO grades three and four. Our findings agree with the results of another, similar prospective randomised trial testing the use of honey for radiation-induced oral mucositis.<sup>11</sup> Our findings were also comparable with the positive results

OCCURRENCE OF MUCOSITIS DURING RADIOTHERAPY									
Mucositis grade	1 wk	2 wks	3 wks	4 wks	5 wks	6 & 7 wks			
Treatment group									
0	17	8	3	3	3	12			
1	3	9	7	6	9	5			
2	0	3	7	8	5	3			
3	0	0	3	3	3	0			
4	0	0	0	0	0	0			
Control group									
0	14	4	0	0	0	5			
1	5	4	4	4	3	4			
2	1	9	9	4	7	4			
3	0	3	4	9	8	5			
4	0	0	3	3	2	2			

TABLE III OCCURRENCE OF MUCOSITIS DURING RADIOTHERAPY

Data represent number of patients. Wk = week

reported from other trials using different approaches for management of radiation-induced oral mucositis. These approaches included the use of povidone iodine oral rinse,<sup>19</sup> prophylactic sucralfate-based mouthwashes containing ciprofloxacin or ampicillin (and clotrimazol),<sup>20</sup> and systemic antifungal prophylaxis with fluconazole.<sup>21</sup>

In patients who receive radiation therapy, the most common clinical infection of the oropharynx is candidiasis.<sup>22</sup> This was confirmed in our study. Following radiotherapy, we found a significantly higher percentage of patients with candida colonisation in the control group than in the treatment group. This prophylactic antifungal effect of honey was similar to that of fluconazole tested as prophylaxis in patients undergoing radiotherapy for head and neck cancer.<sup>21,23</sup> In addition, honey successfully eliminated potentially pathogenic microbial flora in treatment group patients, compared with controls. This finding confirms the antibacterial action of honey.

#### Conclusion

The results of our trial show that prophylactic use of pure natural honey was effective in reducing mucositis resulting from radiochemotherapy in patients with head and neck cancer. Honey differs from other agents in that it is simple, safe and inexpensive. Further studies are necessary to confirm the role and define the optimal dosage and concentration of prophylactic honey in the management of this morbidity.

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