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Topical application of honey in the management of radiation mucositis. A Preliminary study

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Abstract *Background:* The aim of this study was to evaluate the effect of pure natural honey on radiation-induced mucositis. *Patients and methods:* Forty patients diagnosed with head and neck cancer requiring radiation to the oropharyngeal mucosal area were divided in to two groups to receive either radiation alone or radiation plus topical application of pure natural honey. 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 60–70 Gy. In the study arm, patients were advised to take 20 ml of pure honey 15 min before, 15 min after and 6 h post-radiation therapy. Patients were evaluated every week for the development of radiation mucositis using the Radiation Therapy Oncology Group (RTOG) grading system. *Main results:* There was significant reduction in the symptomatic grade 3/4 mucositis among honey-treated patients compared to controls; i.e. 20% versus 75% (p 0.00058). The compliance of honey-treated group of patients was better than controls. Fifty-five percent of patients treated with topical honey showed no change or a positive gain in body weight compared to 25% in the control arm (p 0.053), the majority of whom lost weight. *Conclusions:* Topical application of natural honey is a simple and cost-effective treatment in radiation mucositis, which warrants further multicentre randomised trials to validate our finding.

Keywords Radiation mucositis · Acute morbidity · Honey · Treatment

Introduction

Management of head and neck cancer has undergone tremendous changes over the past 3 decades, with emphasis on organ preservation and multi-modality management, including use of chemo-irradiation. The latter approach is always associated with increased toxicity due to mucositis, resulting in non-compliance to radiotherapy. Every year, about 500,000 newly diagnosed head and neck cancer cases are discovered world wide [1]. The majority of these patients receive surgery, radiotherapy, or both. Radio-chemotherapy may be given in the more advanced stages in patients in good general condition. However, the degree of acute radiation morbidities depends upon the type and technique of chemotherapy and radiotherapy.

Radiation-induced mucositis is a normal acute side effect of radiotherapy treatment. Exposure of ionising radiation to oral, pharyngeal and laryngeal mucosa gives rise to radiation epithelitis towards the second and third weeks of conventional fractionated radiotherapy [2]. Severe radiation mucositis leads to ulceration and painful dysphagia that leads to poor quality of life and treatment discontinuation. The intensity of mucositis depends on the field size, interval between fractions, dose-per-fraction, previous exposure to chemotherapy, concurrent chemotherapy or co-morbid medical conditions like diabetes mellitus or connective vascular disorders. The development of oral mucositis is an inevitable accompaniment of radiation therapy to the head and neck region. At least 50% of patients will experience grade 3 mucositis

when 66–70 Gy radiation are delivered to large mucosal surfaces in 6–7 weeks with 1.8–2 Gy per fraction [3, 4, 5, 6]. There are numerous means to reduce incidence of radiation mucositis. The most common technique is to protect the unaffected mucosa by lead shields, use of conformation therapy, use of mouth bites, decreasing dose-per-fraction and deliberate use of treatment breaks [7]. The above principles do not suit in certain circumstances, like large tumour volume and possible development of tumour resistance due to long treatment interval.

The treatment of radiation-induced mucositis is not well established. However, many agents like topical sucralfate [8], subcutaneous or topical granulocyte macrophage colony stimulating factors (GM-CSF) [9, 10], prostaglandin-E analogue misoprostol [11], topical corticosteroids [12] and parenteral radio-protector amifostine [13] have been tried with various response rates. Currently studies are attempting to find newer agents that are effective, safe and easy to use.

Honey is the by-product of flower nectar and the upper aero-digestive tract of the honeybee, which become concentrated by the dehydration process inside the beehive. Though honey is an age-old remedy from the time of Egyptian civilisation, very recently it has found place in modern medicine [14, 15]. Honey has been found effective in burn wounds, oral infections and acceleration of surgical wound healing [16, 17, 18]. Honey has antibacterial properties and enhances epithelization, thereby improving wound healing [19]. Researchers found a natural resin from honey, which is a potent inhibitor of human colon adenocarcinoma cell growth, carcinogenic induction, and biochemical and para-neoplastic lesion changes in rat colon [20]. We have used natural honey for the treatment of radiation mucositis to enhance epithelization of the mucosa, thereby reduce morbidity.

Patients and methods

From November 2000 to October 2001, 40 patients undergoing radiotherapy to the head and neck region received either topical application of natural honey along with radiotherapy or radiotherapy alone. All treatment parameters were recorded on a special entry form. Informed consent was obtained before starting radiotherapy. Further, patients with prior or concurrent chemotherapy, previous radiotherapy or presence of systemic disease were excluded. All patients were subjected to oro-dental evaluation before and after radiotherapy.

Radiotherapy

Radiotherapy was administered using a 6-MV linear accelerator. Tumour volumes were assessed prior to simulation and adequate margins were taken depending upon the type of malignancy. Usually, parallel-opposed fields were used, and tumour dose was calculated at the mid-plane. In multi-field technique, individual dose calculation technique was used. Conventional fractionated radiation was delivered to the tumour volume at a dose rate of 2 Gy per fraction, treating five fractions per week to a total period of 6–7 weeks. Individualised thermoplastic casts were made to treat tumours of the mobile parts of head and neck areas. External beam radiotherapy was delivered in three phases using the shrinking field technique.

Assessment of tumour response and complication development was monitored weekly at the usual radiotherapy review clinic. Body weight recording and full blood-count examination was performed weekly. Baseline liver function test, kidney function test, and blood sugar levels were estimated before and after completion of radiotherapy. Development of mucositis was assessed using clinical and mirror examination of the mucosa. Radiation Therapy Oncology Group (RTOG) grading system was utilised to grade mucositis [21]. Treatment delays or gaps were recorded in cases where mucositis became intolerable.

Patient recruitment

Twenty patients were allocated equally to one study arm and another 20 to the control arm by computer-generated random numbers. In the treatment arm, topical natural honey was applied to the mucosa. Patients were asked to take 20 ml of natural honey before radiotherapy, 20 ml after radiotherapy and 20 ml 6 h after therapy. They were advised to rinse honey on the oral mucosa and then to swallow slowly to smear it on the oral and pharyngeal mucosa. The above treatment was advised throughout the course of radiotherapy. Both treatment and control-arm patients were advised on adequate fluid intake, supplementation with a high-protein diet and oro-dental care.

Quality control of honey

The main flower involved in the collection of nectar was the tea plant (*Camellia sinensis*) available near the Cameron Highland of peninsular Malaysia. This extract was filtered and supplied as raw or pure honey for the trial. The honey was subjected to chemical analysis, pH, density and viscosity measurement. A thin layer chromatography was used for the chemical analysis. The agent was extracted with potassium ether, chloroform, ethyl alcohol, methyl alcohol and developed to meet $MeOH:H_2O:CHCl3$ proportion of 50:10:64. Vanillin sulphuric acid test was done to determine glycoside compounds. Microbiological assay was done against pathogenic organisms at pure, 1:2, 1:4 and 1:8 dilutions respectively. Culture of *Pseudomonas aeruginosa, Streptococcus pyogenes, Staphylococcus aureus, and Escherichia coli* were plated on agar plate. A filter disc was placed on the medium. About 30 µl of neat and 1:2, 1:4 and 1:8 diluted honey was placed on the disk. The medium was incubated for 18 h and the inhibition zone was measured.

Toxicity criteria

Development of oral and pharyngeal mucositis was graded as 0 for no change, 1 for mucosal erythema, 2 for studded mucositis, 3 for confluent mucositis not requiring intervention and 4 for ulceration, which necessitated treatment break as per specifications of the RTOG grading system [21].

Analysis

All patient demographic, treatment related and morbidity scores were analysed using Microsoft-Excel software. The difference between the morbidities, nutritional parameters, treatment breaks and total duration of mucositis, etc. was compared using chi-square comparison from EPI Info 2000 software.

Table 1 Patients characteristics

Total number of patients	40
Controls	20
Study arm	20
Male:female ratio	
Controls	8:12
Study arm	15:5
Age distribution (years)	
Controls	14 (minimum) 54 (median) 78 (maximum)
Treatment arm	19 (minimum) 63 (median) 89 (maximum)

Tumor location/TNM classification

T category	Control	Study arm
T1	00	01
T2	01	01
T3	05	03
T4	12	12
N0	04	06
N1	06	03
N2	04	02
N3	03	04
M1	00	02
Location		
Nasopharynx	06	03
Larynx	01	06
Paranasal sinus	04	01
Thyroid	03	03
Oral cavity	03	03
Oropharynx + hypopharynx	01	04
Parotid, mastoid	02	00
Body weight		
Median [in kilograms]	45	52
Mean [in kilograms]	46.5	50
Range [in kilograms]	33–68	28–75
Mean radiation field area	32 cm^2	53.4 cm^2

Results

The study was completed in October 2001, and all cases received radiotherapy as planned. Primary tumours were distributed in nasopharynx (9), larynx (7), paranasal sinuses (7), thyroid (5) and other miscellaneous sites (12) (Table 1), The honey was subjected to microbiological assay to evaluate its antibacterial potency before administration. It showed good inhibition of bacterial growth proportionate to concentration. Organisms like *P. aeruginosa, E. coli, S, pyogenes and S. aurious* colonies showed good growth inhibition in vitro. The zone of inhibition showed decreasing trend on dilution. Chemical analysis showed a pH of 4.35 and contained five compounds of terpenoids, tetrapenoids, trace elements, nitrogenous compounds, glycosides and sugars. Viscosity was 3.905 N and density 1.384 g/ml. All patients in the treatment arm received honey throughout their radiotherapy course. There were no complications related to administration of pure honey. Blood sugar monitoring revealed no change following administration. Sixteen patients showed some form of radiation mucositis compared to 19 in the control arm. The difference in grade 3/4 mucositis was 20% and 75% respectively in the treatment and control arm (Table 2). The above finding

Table 2 Oral mucositis in honey-treated and control groups *NS* not significant

	Controls	Study group	Remarks
Number of patients	20	20	NS
Patients with mucositis	16	19	NS
Patients with grade 3/4 mucositis	04	15	0.0005838
Mean grade of mucositis	3.05	3.3	NS
Mean onset of mucositis (week)	3	3	NS
Mean total duration of mucositis (days)	07	07	NS
Negative body weight (in kilograms)	09	11	NS
Static or positive body weight (in kilograms)	11	05	0.0532299
Mucositis-related treatment interruptions in days	04/20	00/20	0.0373

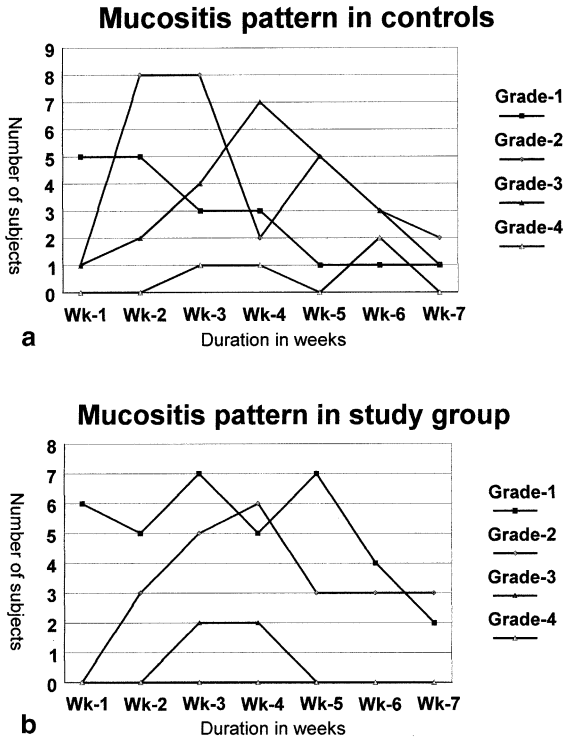

Fig. 1 **a** Graph showing pattern of various grades of mucositis in controls. **b** Graph showing pattern of mucositis in study group

Table 3 Distribution of mucositis during radiotherapy course

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Total
Controls								
G0	16	05	04	07	09	11	16	68
G1	05	05	03	03	01	01	01	18
G2	01	08	08	02	05	03	02	29
G3	01	02	04	07	05	03	01	23
G4	00	00	01	01	00	02	00	04
Treatment								
G0	14	12	06	07	10	13	17	79
G1	06	05	07	05	07	04	02	36
G2	00	03	05	06	03	03	01	21
G3	00	00	02	02	00	00	00	04
G4	00	00	00	00	00	00	00	00

was statistically significant ($p<0.00058$). Median mucositis grade was grade 2 in controls and grade 1 the honey-treated groups; maximum onset was observed during the third week in both arms (Table 3, Fig. 1a, b). In the evaluation of weekly body weight, the variation was +2–9 for controls and +9–8 for the study group. Interestingly, 55% of the honey-treated patients showed either static or positive weight gain during radiotherapy in comparison to 25% in the control arm ($p<0.05$). The difference in the mucositis patterns is illustrated in Fig. 1a, b, which showed significant reduction in grades 3 and 4 mucositis in the honey-treated group. As a consequence of radiation mucositis, treatment of four patients (20%) was interrupted among controls compared to none in the study arm. Treatment interruptions in days were 8, 4, 6 and 9 in controls. These patients required either or both enteral and parenteral fluid and nutritional supplementations, along with topical anaesthetics and analgesics.

Discussion

This study has shown encouraging results for the prevention of symptomatic radiation mucositis. Though there was no significant change in grade 1 and 2 mucositis, grade 3/4 mucositis was significantly reduced in the treatment arm. At present, there is no study on honey available to compare with our study; however, compared to a prospective randomised trial in the use of povidone iodine oral rinse, results are similar [22]. Also, we found an interesting observation regarding the change in body weight. In the study arm, 55% of patients showed either static or a gain in body weight during radiotherapy compared to 25% of patients on the control arm.

Radiation-induced mucositis is a normal accompaniment of radical radiotherapy to the head and neck area. Normally, the oral mucosa has a relatively high cell-turnover rate. Exposure to ionising radiation leads to mucosal erythema, small whitish patches and ultimately results in confluent mucositis. In the later phases, oral ulceration and bleeding become a dose-limiting toxicity. Mucositis is 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 colonisation in the oral mucosa can aggravate the pre-existing mucositis. Endotoxins 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 [23, 24].

Much has been reported about mucositis and stomatitis, but a lack of consistency and use of grading criteria and reporting standards makes it very difficult to draw comparative conclusions concerning toxicity end points among various trials. The lack of standardisation remains problematic, in spite of recent efforts to improve grading and reporting [2].

In 1981, the World Health Organization published grading criteria for 28 acute toxicities, including mucositis [25]. Subsequently, the National Cancer Institute's (NCI) common toxicity criteria was published in 1983, which included 49 chemotherapy related toxicity criteria scales along with mucositis [2]. The following year, an acute radiation toxicity system was published by the RTOG [21], followed by different toxicity criteria from the Eastern Cooperative Oncology Group (ECOG) and the South-West Oncology Group (SWOG). The latter two groups were basically used for chemotherapy-induced toxicities. Hence, RTOG is one of the common toxicity scoring system to quantify radiation-induced mucositis.

The basis of management of radiation mucositis is targeted to its four defined pathogeneses: The most important is to check basal cell layer growth by modifying transforming growth factor β3 [26]. The second mechanism is stimulation of epithelization, thereby encouraging rapid recovery of cell loss [27, 28]. Third is the

chemical protection of mucosa using the Amino-Thiol group of compounds like amifostine [29]. Last but not least is the physical protection of oral mucosa by shield use, conformation therapy or intensity modulated radiotherapy [30]. Local antibiotics in the form of lozenges have been tried with the hope of preventing bacterial colonisation and reducing inflammation of damaged mucosa. Low-energy He/Ni laser treatment may promote the proliferation of mucosal cells, and wound healing has been tried for the treatment of chemotherapy/radiotherapy-induced mucositis [31]. The above treatments are cumbersome and produces no consistent results.

Honey results primarily from the transformation and concentration of nectars from flowers by two processes: the interaction with the upper digestive tract secretion of the honeybees and concentration by water loss (>80%) in beehives. There are four types honey available for study, i.e. sunflower, acacia, floral and wild floral type [32]. They contain moisture, fructose, glucose, sucrose, maltose and other compounds, along with trace elements [33]. Honey quality basically depends upon source and dilution. In this study, we used honey derived mainly from tea plant (*Camellia sinensis*) flowers grown in Malaysia. 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. Coating a wound with honey retards tissue oxygenation by sealing the damaged mucosa from air (oxygen). This could dampen pain within 30 seconds after application.

In the recent past, honey has been used for the treatment of burn wound, infected surgical wounds, childhood diarrhoea, eye infections, etc [15, 34]. The philosophy of using honey in radiation mucositis was derived from the basic research and clinical observation of rapid epithelization in tissue injuries [35, 36]. In an experimental study by Bergman and co-workers, un-boiled topical honey was applied to the open wound and the histopathological response was documented sequentially. The wound of the honey-treated animals healed much faster than the wound of control animals (p 0.001). According to this study, un-boiled honey seems to accelerate wound healing when applied topically due to its energy producing properties, its hygroscopic effect on the wound and its bacteriostatic properties. Important factors that influences the effectiveness of honey are: (1) Its hygroscopic nature, (2) Acidic pH prevents bacteria growth when applied to the mucosa; (3) Inhibin (hydrogen peroxide) converted from glucose oxydase and gluconic acid; (4) Enzymes (growth factors?) and tissue-nutritive minerals and vitamins help repair tissue directly.

Bacterial growth in the oral cavity can aggravate the effect of radiation mucositis. A study conducted by Al-Tikriti et al. demonstrated that oropharyngeal flora contribute to radiation-induced mucositis [23]. Endotoxins released by gram-negative bacilli are potent mediators of an inflammatory process [24]. Use of topical antibiotics like benzydamine has shown slight improvement mucositis control. Another study by Rhan et al. used povidone-iodine oral rinse to reduce chemo-radiotherapy-induced mucositis. In their small randomised trial, mucositis severity and duration was reduced compared to controls treated with placebo (70% versus 100%) [22]. The antibacterial property of honey depends upon its concentration [37]. In our study, we found bacterial growth inhibition around a drop of undiluted honey, but bacterial growth inhibition is inversely related to its dilution. Hence, the reduction of radiation mucositis in honey-treated patients might be due to the bacteriostatic effect of viscid honey. The same osmolarity-based bacteriostasis was demonstrated in other studies [38, 39]. 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 [40]. In a recently published report from the Russian Academy of Medical Science, patients treated with honey laminolact in uterine cancer patients undergoing radiotherapy showed significant decrease in the severity of radiation-induced intestinal morbidity [41].

In conclusion, from our small comparative study, we found usefulness of pure natural honey in the management of symptomatic radiation mucositis. As this agent is effective in radiation mucositis, the same treatment could be useful in the management of chemotherapy induced oral stomatitis/mucositis and in mucositis of bone marrow transplant patients. The philosophy of management in the above conditions is similar. The further issue in the use of medicinal honey is quality assurance of natural honey – which might be different in different geographic locations – and the source of pollens. As the future multi-modality approach to cancer lies in chemo-radiotherapy and altered fractionation schemes, prevention of oral mucositis is very important in its management. Honey could be a simple and inexpensive agent for the management of this morbidity. However, further randomised studies are essential to validate our findings.

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